F2

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 487/04, A61K 31/519, A61P 31/18 **A1**

(11) International Publication Number: **WO 00/42043**

(43) International Publication Date: 20 July 2000 (20.07.00)

(21) International Application Number: PCT/US00/00578

(22) International Filing Date: 10 January 2000 (10.01.00)

(30) Priority Data:
09/229,391 11 January 1999 (11.01.99) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 09/229,391 (CON)
Filed on 11 January 1999 (11.01.99)

(71) Applicant *(for all designated States except US)*: THE REGENTS OF THE UNIVERSITY OF MICHIGAN [US/US]; 3003 S. State Street, Ann Arbor, MI 48019 (US).

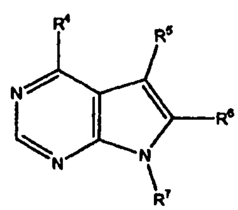
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: TOWNSEND, Leroy, B. [US/US]; 3317 E. Dobson Place, Ann Arbor, MI 48105 (US). DRACH, John, C. [US/US]; 1372 Barrister Road, Ann Arbor, MI 48105 (US).

(74) Agents: KONSKI, Antoinette, F. et al.; Baker & McKenzie, 660 Hansen Way, Palo Alto, CA 94304 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PYRROLO[2,3-*d*]PYRIMIDINES AS ANTIVIRAL AGENTS



(I)

(57) Abstract

This invention relates to a novel class of 4,5,6,7-substituted non-nucleoside, non-phosphorylatable pyrrolo[2,3-*d*]pyrimidines which exhibit both significantly lower levels of cytotoxicity and superior antiviral activity than known nucleoside, non-nucleoside, and non-nucleoside, non-phosphorylatable pyrrolo[2,3-*d*]pyrimidine derivatives, particularly against human DNA viruses such as cytomegalovirus (HCMV), herpes simplex virus type 1 (HSV-1). These compounds are represented by formula (I) wherein: R^4 is $-NR_1R_2$ or oxo; R^5 is $-CN$ or $-CSNR_1R_2$, or $-CONR_1R_2$; R^6 is $-H$, or halo, or $-NR_1R_2$; wherein R_1 and R_2 are independently $-H$ or an aliphatic group; and R^7 is of the formula R_3-Ar, wherein R_3 is an aliphatic group and Ar is an unsubstituted aryl or an aryl independently substituted with halo, nitro, amino, or aliphatic groups; provided that when R^5 is a $-CN$ or $-CSHN_2$, and R^6 is a $-H$ or $-NH_2$; and Ar is a $-C_6H_5$ or a phenyl substituted with only one aliphatic group, R_3 is an aliphatic group other than methyl such that $-R_3$ is not a $-CH_2$; and pharmaceutically acceptable salts, prodrugs and derivatives thereof.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PYRROLO[2,3-*d*]PYRIMIDINES AS ANTIVIRAL AGENTS

STATEMENT OF RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH

This invention was made in part with Government support under contract number NO1-AI72641 awarded by the National Institute of Allergy and Infectious Diseases. The United States government has certain rights in this invention.

TECHNICAL FIELD

The present invention relates to new non-phosphorylatable, non-nucleoside pyrrolo[2,3-*d*]pyrimidines and their use in the treatment of viral infections.

BACKGROUND OF THE INVENTION

Broad spectrum antiviral activity of pyrrolo[2,3-*d*]pyrimidine nucleosides such as tubercidin, sangivamycin and toyocamycin and some substituted derivatives has been previously reported. Activity of those compounds against specific viruses, such as RNA rhinovirus and DNA herpes simplex virus type 1 and type 2 has also been reported. See, for example, Bergstrom, D. E. *et al.*, *J. Med. Chem.* 27:285-292 (1984); and DeClercq, E. *et al.*, *Antimicrob. Agents Chemother.* 29:482-487 (1986).

Pyrrolo[2,3-*d*]pyrimidine nucleosides are particularly attractive as potential antiviral agents because of their stability toward the action of two major enzymes of bioactive purine nucleoside inactivation, deamination by adenosine deaminase and glycosidic bond cleavage by purine nucleoside phosphorylases. Unfortunately, many of the pyrrolo[2,3-*d*]pyrimidine nucleosides which have been previously described as having potential antiviral activity also exhibit unacceptable levels of cytotoxicity, thereby diminishing their usefulness in treatment of viral infections.

A number of pyrrolo[2,3-*d*]pyrimidine nucleoside derivatives which exhibit improved antiviral activity and more acceptable levels of cytotoxicity than tubercidin, sangivamycin, toyocamycin and thiosangivamycin have been reported. These prior art pyrrolo[2,3-*d*]pyrimidine nucleoside derivatives are described below.

Townsend *et al.* (U.S. Patent No. 4,892,865) disclose the use of, *inter alia*, several 4-amino-pyrrolo[2,3-*d*]pyrimidine-5-carbonitriles and 4-aminopyrrolo [2,3-*d*]pyrimidine-5-thiocarboxamides substituted at the 7-position with 2',3'-dideoxy-2',3'-didehydro-β-D-ribofuranose and 2',3'-dideoxyribofuranose as antiviral agents.

Renau *et al., Bioorg. & Med. Chem. Lett.* 2:1755-1760 (1992), disclose the use of, *inter alia*, 4-amino-pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamides and 4-amino-pyrrolo[2,3-*d*]pyrimidine-5-carbonitriles substituted at the 7-position with β-D-ribofuranose as antiviral agents.

A number of pyrrolo[2,3-*d*]pyrimidine non-nucleoside derivatives that exhibit improved antiviral activity and more acceptable levels of cytotoxicity than tubercidin, sangivamycin, toyocamycin and thiosangivamycin as well as the nucleoside derivatives described above have been reported. These prior art pyrrolo[2,3-*d*]pyrimidine non-nucleoside derivatives are described below.

Townsend *et al.* (U.S. Patent Nos. 4,927,830 and 4,968,686) disclose the use of, *inter alia*, several 4-amino-pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamides and 4,6-diamino-pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamides variously substituted at the 7-position with $-CH_2OCH(CH_2OH)_2$, $-CH_2OCH_2CH_2OH$ and $-CH(CH_2OH)(OCH(CH_2OH)_2)$ as antiviral agents.

Gupta *et al., J. Med. Chem.* 32:402-408 (1989), disclose the use of, *inter alia*, several 4-amino-pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamides and 4-amino-pyrrolo[2,3-*d*]pyrimidine-5-carbonitriles variously substituted at the 7-position by $-CH_2OCH(CH_2OH)_2$ and $-CH(CH_2OH)(OCH(CH_2OH)_2)$ as antiviral agents.

Gupta *et al., J. Med. Chem.* 32:1420-1425 (1989), disclose the use of, *inter alia*, several 4-amino-pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamides and 4-amino-pyrrolo[2,3-*d*]pyrimidine-5-carbonitriles substituted at the 7-position by $-CH_2OCH_2CH_2OH$ as antiviral agents.

Renau *et al., Antiviral Res.* 19:15-28 (1992), disclose the use of 4-amino-pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide and 4-amino-pyrrolo[2,3-*d*]pyrimidine -5-carbonitrile substituted at the 7-position by $-CH_2OCH_2CH_2OH$ as antiviral agents.

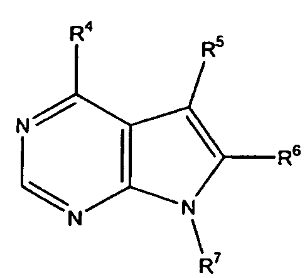
Swayze *et al.*, *Nucleosides and Nucleotides* 11:1507-1527 (1992), disclose the use of, *inter alia*, 4,6-diamino-pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamides and 4,6-diamino-pyrrolo[2,3-*d*]pyrimidine-5-carbonitriles variously substituted at the 7-position by $-CH_2OCH_2CH_2OH$ and $-CH_2OCH(CH_2OH)_2$ as antiviral agents.

A limited number of pyrrolo[2,3-*d*]pyrimidine non-nucleoside, non-phosphorylatable derivatives which exhibit improved antiviral activity and more acceptable levels of cytotoxicity than tubercidin, sangivamycin, toyocamycin and thiosangivamycin as well as the nucleoside derivatives described above have been reported.

For example, Renau *et al.*, *Biorg. & Med. Chem. Lett.* 2:1755-1760 (1992), disclose the use of, *inter alia*, several 4-amino-pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamides and 4-amino-pyrrolo[2,3-*d*]pyrimidine-5-carbonitriles variously substituted at the 7-position with $-CH_2OCH_2CH_2OH$, $-CH_2OCH(CH_2\text{-}OH)_2$, CH_3, -$CH_2CH{=}CH_2$, and $-CH_2CH_2CH_3$ as antiviral agents.

BRIEF DESCRIPTION OF THE INVNENTION

One aspect of the present invention relates to a novel class of 4,5,6,7-substituted non-nucleoside, non-phosphorylatable pyrrolo[2,3-*d*]pyrimidines that exhibit both significantly lower levels of cytotoxicity and superior antiviral activity than known nucleoside, non-nucleoside, and non-nucleoside, non-phosphorylatable pyrrolo[2,3-*d*]pyrimidine derivatives, particularly against human DNA viruses such as cytomegalovirus (HCMV) and herpes simplex virus type 1 (HSV-1). Many of these compounds are represented by the following formula:



wherein

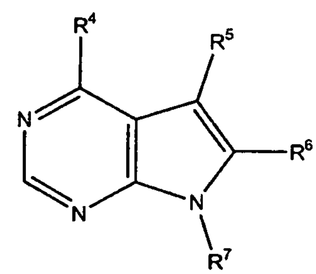
R^4 is NR_1R_2 or oxo;

R^5 is -CN, -CSNR$_1$R$_2$, or -CONR$_1$R$_2$;

R^6 is -H, or halo, or NR$_1$R$_2$;

wherein R_1 and R_2 are independently -H or an aliphatic group, and R_7 is of the formula R_3-Ar, wherein R_3 is an aliphatic group and Ar is an unsubstituted aryl or an aryl independently substituted with halo, nitro, amino, or aliphatic groups; provided that when R^5 is a -CN or -CSNH$_2$, and R^6 is a -H or -NH$_2$, and Ar is a-C_6H_5 or a phenyl substituted with only one aliphatic group, R_3 is an aliphatic group other than methyl such that -R_3- is not a -CH$_2$-; and pharmaceutically acceptable salts, prodrugs and derivatives thereof. In one embodiment, R^5 is not –CONH$_2$.

The present invention also provides a compound having the structure:



wherein:

R^4 is -NR$_1$R$_2$ or oxo;

R^5 is -CN or -CSNR$_1$R$_2$;

R^6 is -H, or halo, or -NR$_1$R$_2$;

wherein R_1 and R_2 are independently -H or an aliphatic group; and R^7 is of the formula R_3-Ar, wherein R_3 is a aliphatic group and Ar is an unsubtstituted aryl or an aryl independently substituted with halo, nitro, amino, or aliphatic groups; provided that when R^6 is a -H or -NH$_2$ and Ar is -C_6H_5 or a phenyl substituted with only one aliphatic group, R_3 independently may or may not be an aliphatic group other than methyl such that -R_3-is not a -CH$_2$-; and pharmaceutically acceptable salts, prodrugs and derivatives thereof.

In one embodiment, R^4 is -NH$_2$; R^5 is-CN and R^6 is -H. In another embodiment, R^4 is -NH$_2$; R^5 is -CSNH$_2$ and R^6 is -H. In yet another embodiment, R^4 is -NH$_2$; R^5 is -

CN and R^6 is $-NH_2$. In yet another embodiment, R^4 is $-NH_2$; R^5 is -CN and R^6 is a halo group. In yet another embodiment, the halo group is a bromo or chloro.

Some embodiments comprise a pyrrolo [2,3-*d*]pyrimidine compound having the following structural features:

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH(CH_3)-C_6H_4$ (1414);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-C_6H_4$-4-F (1429);

R^4 is NH_2; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-C_6H_4$-4-Cl (1444);

R^4 is NH_2; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-C_6H_4-4-NO_2$ (1360);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is$-CH_2-C_6H_4-3-NO_2$ (1362);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-(CH_2)_3-C_6H_5$ (1350);

R^4 is $-NH_2$; R^5 is - $CSNH_2$; R^6 is -H; and R^7 is $-CH_2-CH_2-C_6H_5$ (1446);

R^4 is $-NH_2$; R^5 is $-CSNH_2$; R^6 is -H; and R^7 is $-CH_2-CH_2-CH_2-C_6H_5$ (1413);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-CH_2-C_6H_5$ (1358 or 1368);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH(CH_3)-C_6H_5$ (1451);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-CH_2-C_6H_5$ (1369);

R^4 is $-NHCH_3$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4-3-NO_2$ (1425);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4-3-NH_2$ (1455);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$ and R^7 is $-CH_2-C_6H_4$-4-F (1365);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4$-4-Cl (1356);

R^4 is NH_2; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4$-4-Br (1389);

R^4 is NH_2; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2C_6H_4-4-NO_2$ (1348);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4-4-NH_2$ (1352);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-CH=CH-CH_2-C_6H_5$ (1372);

R^4 is$-NH_2$; R^5 is-CN; R^6 is $-NH_2$; and R^7 is $-CH_2-CH=CH-CH_2-C_6H_5$ (1329);

R^4 is -oxo; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-CH_3$ (1441);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH(CH_3)-C_6H_5$ (1363);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4$-4-F (1353);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4$-4-Cl (1355);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4$-3-Cl (1461);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_3-3,4-(Cl)_2$ (1462);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-Br$ (1373);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-NO_2$ (1374);

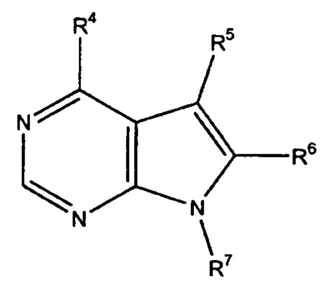
R^4 is $-NH-CH_3$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-CH_2-C_6H_5$ (1463);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-CH_2-C_6H_5$ (1351);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-(CH_2)_3-C_6H_5$ (1347); and

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-CH=CH-C_6H_5$ (1361).

In one embodiment, the present invention provides for a compound having the structure:



wherein:

R^4 is $-NR_1R_2$ or oxo;

R^5 is $-CONR_1R_2$;

R^6 is -H, or halo, or $-NR_1R_2$;

wherein R_1 and R_2 are independently -H or an aliphatic group; and R^7 is of the formula R_3-Ar, wherein R_3 is an aliphatic group and Ar is an unsubstituted aryl or an aryl independently substituted with halo, nitro, amino, or aliphatic groups; and pharmaceutically acceptable salts, prodrugs and derivatives thereof.

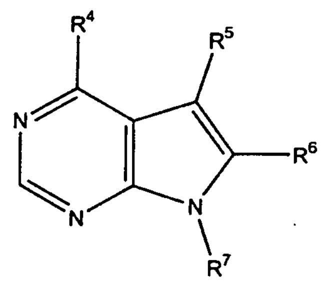
In one embodiment, R^4 is $-NH_2$; R^5 is $-CONR_1R_2$ and R^6 is a halo group. In another embodiment, R^1 and R^2 are independently -H or an aliphatic group and the halo group is a chloro or bromo. In yet another embodiment, R^4 is $-NH_2$; R^5 is $-CONH_2$; and R^6 is bromo.

Some embodiments comprise a pyrrolo[2,3-*d*]pyrimidine compound having the following structural features:

R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2-C_6H_5$ (659);

R^4 is NH_2; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH(CH_3)-C_6H_5$ (1428);
R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2C_6H_4-2-CH_3$ (836);
R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2-C_6H_4-3-CH_3$ (826);
R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2-C_6H_4-4-CH_3$ (658);
R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2-C_6H_4-4-C(CH_3)_3$ (845);
R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2-C_6H_4-4-OCH_3$ (839);
R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2C_6H_4-4-F$ (1419);
R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2-C_6H_4-4-NO_2$ (1412);
R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2-C_6H_4-3-NO_2$ (1421);
R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-Cl$ (1443);
R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-CH_3$ (1427);
R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2-CH_2-C_6H_5$ (1396);
R^4 is NH_2; R^5 is $-CONH_2$; R^6 is -Br; and R^7 is $-CH_2-CH_2-C_6H_5$ (1409); and
R^4 is NH_2; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2-CH_2-CH_2-C_6H_5$ (1362).

Another embodiment provides for a compound having the structure



wherein:

R^4 is $-NR_1R_2$ or oxo;

R^5 is -CN, or $-CSNR_1R_2$ or $-CONR_1R_2$;

R^6 is halo;

wherein R_1 and R_2 are independently -H or an aliphatic group; and R^7 is of the formula R_3-Ar, wherein R_3 is an aliphatic group and Ar is an unsubstituted aryl or an aryl independently substituted with halo, nitro, amino, or aliphatic groups; provided that when R^6 is bromo and Ar is $-C_6H_5$ or a phenyl substituted with only one aliphatic group,

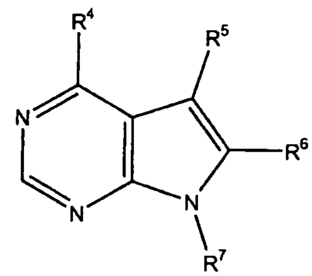
R_3 independently may or may not be an aliphatic group other than methyl such that $-R_3-$ is not a $-CH_2-$; and its pharmaceutically acceptable salts, prodrugs and derivatives thereof. In one embodiment, R^5 is not $-CONH_2$.

In one embodiment, R^4 is $-NH_2$; R^5 is -CN or $-CONR_1R_2$ and R^6 is a halo group. In another embodiment, R_1 and R_2 are independently -H or an aliphatic group and the halo group is a chloro or bromo.

Some embodiments comprise a pyrrolo[2,3-*d*]pyrimidine compound having the following structural features:

R^4 is -oxo; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-CH_3$ (1441);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH(CH_3)-C_6H_5$ (1363);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-F$ (1353);
R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-Cl$ (1443);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-Cl$ (1355);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-3-Cl$ (1461);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_3-3,4-(Cl)_2$ (1462);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-Br$ (1373);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-NO_2$ (1374);
R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-CH_3$ (1427);
R^4 is $-NH-CH_3$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-CH_2-C_6H_5$ (1463);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br and R^7 is $-CH_2-CH_2-C_6H_5$ (1351);
R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is Br; and R^7 is $-CH_2-CH_2-C_6H_5$ (1409);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-(CH_2)_3-C_6H_5$ (1347); and
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-CH=CH-C_6H_5$ (1361).

Yet another embodiment provides for a compound having the structure:



wherein:

R^4 is $-NR_1R_2$ or oxo;

R^5 is -CN, or $-CSNR_1R_2$, or $-CONR_1R_2$;

R^6 is -H, or halo, or $-NR_1R_2$;

wherein R_1 and R_2 are independently -H or an aliphatic group; and R^7 is of the formula R_3-Ar, wherein R_3 is an aliphatic group and Ar is an aryl independently substituted with halo, nitro, amino groups; and pharmaceutically acceptable salts, prodrugs and derivatives thereof. In one embodiment, R^5 is not $-CONH_2$.

In one embodiment, R^4 is $-NH_2$; R^5 is -CN or $-CONR_1R_2$; R^6 is -H or a halo group. In another embodiment, R_1 and R_2 are independently -H or an aliphatic group and the halo group is a chloro or bromo.

Some embodiments comprise a pyrrolo[2,3-*d*]pyrimidine compound having the following structural features:

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-C_6H_4-4-F$ (1429);

R^4 is NH_2; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-C_6H_4-4-Cl$ (1444);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-C_6H_4-4-NO_2$ (1360).

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-C_6H4-3-NO_2$ (1362);

R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2-C_6H_4-4-F$ (1419);

R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2-C_6H_4-4-NO_2$ (1412);

R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2-C_6H_4-3-NO_2$ (1421);

R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-Cl$ (1443);

R^4 is $-NH_2$; R^5 is-CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-Cl$ (1388) or (1355);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4$-3-Cl (1461);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_3$-3,4-$(Cl)_2$ (1462);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4$-4-Br (1373);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4$-4-NO_2 (1331);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4$-4-NO_2 (1374);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$ and R^7 is $-CH_2-C_6H_4$-4-F (1365);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4$-4-Cl (1356);

R^4 is NH_2; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4$-4-Br (1389);

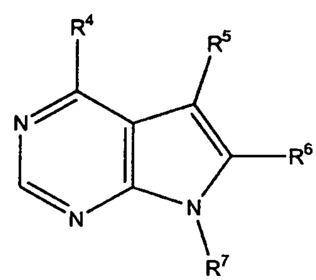
R^4 is NH_2; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4$-4-NO_2 (1348);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4$-4-NH_2 (1352);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4$-3-NO_2 (1425); and

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4$-3-NH_2 (1455).

In one aspect, the present invention provides for a compound having the structure



wherein:

R^4 is $-NR_1R_2$, or oxo;

R^5 is -CN, or $-CSNR_1R_2$, or $-CONR_1R_2$;

R^6 is -H, or halo, or $-NR_1R_2$;

wherein R_1 and R_2 are independently -H or an aliphatic group; and R^7 is of the formula R_3-Ar, wherein R_3 is an aliphatic group and Ar is an unsubstituted aryl or an aryl independently substituted with halo, nitro, amino, or aliphatic groups; provided that R_3 is an aliphatic group other than methyl such that $-R_3-$ is not a $-CH_2-$; and

pharmaceutically acceptable salts, prodrugs and derivatives thereof. In one embodiment, R^5 is not
–$CONH_2$.

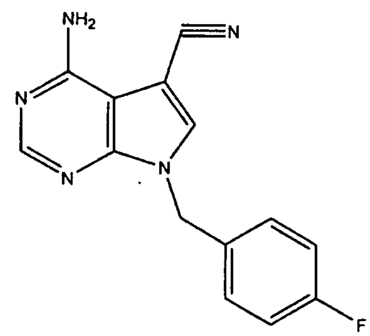
In one embodiment, R^4 is -NH_2; R^5 is -CN or -$CONR_1R_2$ or -$CSNR_1R_2$; and R^6 is -H or -NH_2, or a halo group. In other embodiment, R_1 and R_2 are independently -H or an aliphatic group and the halo group is a chloro or bromo.

Some embodiments comprise a pyrrolo[2,3-*d*]pyrimidine compound having the following structural features:

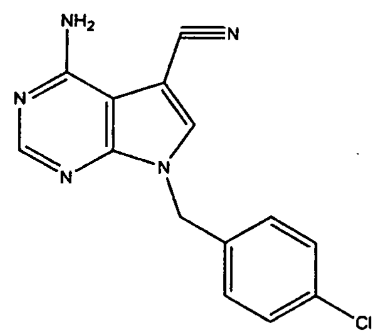
R^4 is -NH_2; R^5 is -CN; R^6 is -Br; and R^7 is -$CH(CH_3)$-C_6H_5 (1363);
R^4 is -NH_2; R^5 is -CN; R^6 is -NH_2; and R^7 is -$CH(CH_3)$-C_6H_5 (1451);
R^4 is -NH_2; R^5 is -CN; R^6 is -H; and R^7 is -CH_2-CH_2-C_6H_5 (1368);
R^4 is -NH_2; R^5 is -$CONH_2$; R^6 is -H; and R^7 is -CH_2-CH_2-C_6H_5 (1396);
R^4 is -NH_2; R^5 is -$CSNH_2$; R^6 is -H; and R^7 is -CH_2-CH_2-C_6H_5 (1446);
R^4 is -NH_2; R^5 is -CN; R^6 is -NH_2; and R^7 is -CH_2-CH_2-C_6H_5 (1369);
R^4 is -NH_2; R^5 is -$CSNH_2$; R^6 is -H; and R^7 is -CH_2-CH_2-CH_2-C_6H_5 (1413);
R^4 is -NH_2; R^5 is -$CONH_2$; R^6 is -H; and R^7 is -CH_2-CH_2-CH_2-C_6H_5 (1376);
R^4 is -NH_2; R^5 is -CN; R^6 is -H; and R^7 is-CH_2-CH_2-CH_2-C_6H_5 (1362);
R^4 is -NH-CH_3; R^5 is -CN; R^6 is -Br; and R^7 is -CH_2-CH_2-C_6H_5 (1463);
R^4 is -NH_2; R^5 is -CN; R^6 is -Br; and R^7 is -CH_2-CH_2-C_6H_5 (1351);
R^4 is NH_2; R^5 is -$CONH_2$; R^6 is -Br; and R^7 is -CH_2-CH_2-C_6H_5 (1409);
R^4 is -NH_2; R^5 is -CN; R^6 is -Br; and R^7 is -$(CH_2)_3$-C_6H_5 (1347);
R^4 is -NH_2; R^5 is -CN; R^6 is -Br; and R^7 is -CH_2-CH=CH-C_6H_5 (1361);
R^4 is -NH_2; R^5 is -CN; R^6 is -NH_2; and R^7 is -CH_2-CH_2-CH_2-C_6H_5 (1350);
R^4 is-NH_2; R^5 is-CN; R^6 is-H; and R^7 is-CH_2-CH=CH-C_6H_5 (1372); and
R^4 is-NH_2; R^5 is-CN; R^6 is-NH_2; and R^7 is -CH_2-CH=CH-C_6H_5 (1329).

The present invention provides for a pharmaceutical composition comprising a therapeutically effective amount of one or more compounds of the above embodiments, their pharmaceutically acceptable salts, prodrugs or derivatives and a pharmaceutically acceptable carrier. Such pharmaceutical compositions can be used to treat or prevent a variety of viral infections such as HCMV, HSV-1, HBV, HCV, among others.

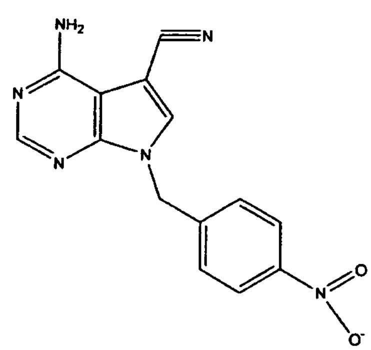
One embodiment of the present invention has a compound having the following structure (1429):



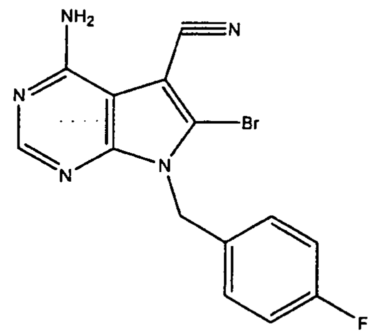
Another embodiment of the present invention has a compound having the following structure (1444):



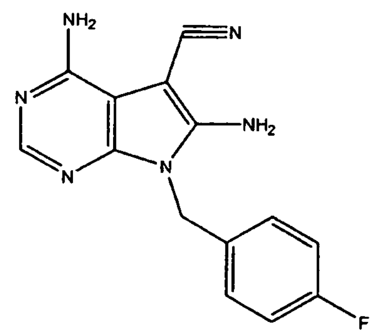
Another embodiment of the present invention has a compound having the following structure (1360):



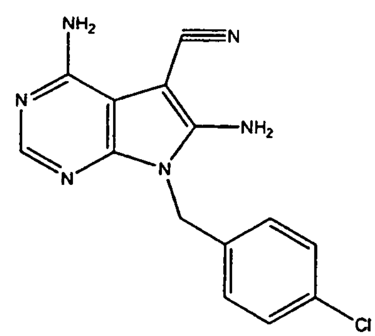
Yet another embodiment of the present invention has a compound having the following structure (1353):



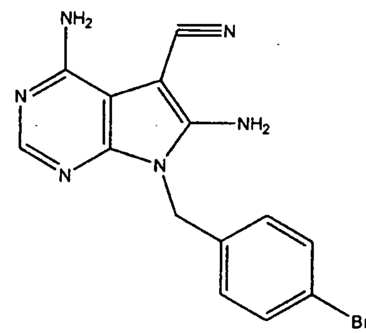
A further embodiment of the present invention has a compound having the following structure (1365):



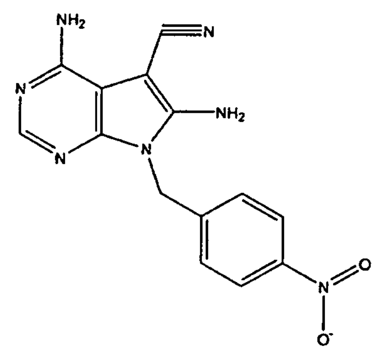
Another embodiment of the present invention has a compound having the following structure (1356):



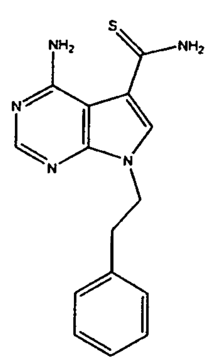
Another embodiment of the present invention has a compound having the following structure (1389):



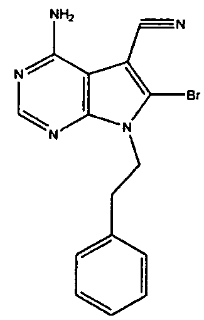
Yet another embodiment of the present invention has a compound having the following structure (1348):



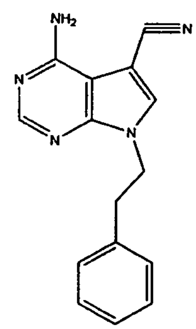
Another embodiment of the present invention has a compound having the following structure (1446):



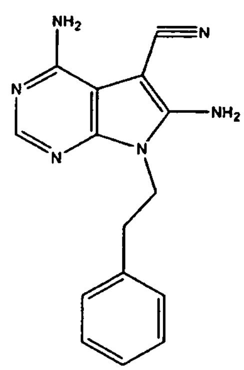
One further embodiment of the present invention has a compound having the following structure (1351):



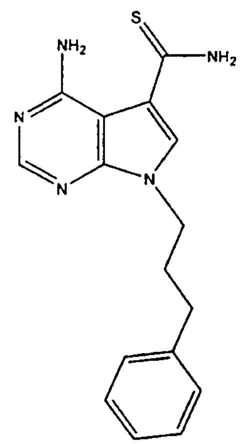
Another embodiment of the present invention has a compound having the following structure (1368):



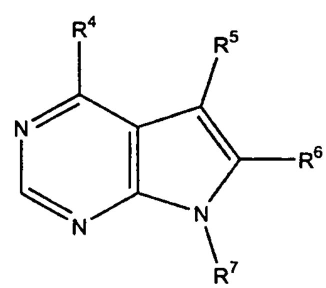
Yet another embodiment of the present invention has a compound having the following structure (1369):



Another specific embodiment of the present invention has a compound having the following structure (1413):



The present invention provides for a method for treating or preventing a viral infection comprising administering an effective amount of one or more compounds of the following structure:



wherein:

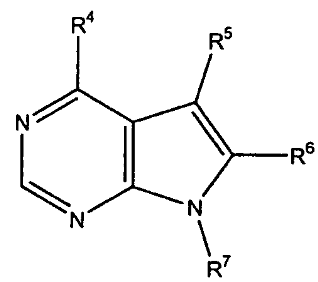
R^4 is $-NR_1R_2$ or oxo;

R^5 is -CN, or $-CSNR_1R_2$, or $-CONR_1R_2$;

R^6 is -H, or halo, or $-NR_1R_2$;

wherein R_1 and R_2 are independently -H or an aliphatic group; and R^7 is of the formula R_3-Ar, wherein R_3 is an aliphatic group and Ar is an unsubstituted aryl or an aryl independently substituted with halo, nitro, amino, or aliphatic groups; and pharmaceutically acceptable salts, prodrugs and derivatives thereof. In one embodiment, R^5 is not $-CONH_2$.

In one embodiment of the above method, the one or more compounds have the following structure:



wherein:

R^4 is $-NR_1R_2$ or oxo;

R^5 is -CN or $-CSNR_1R_2$;

R^6 is -H, or halo, or $-NR_1R_2$;

wherein R_1 and R_2 are independently -H or an aliphatic group; and R^7 is of the formula R_3-Ar, wherein R_3 is an aliphatic group and Ar is an unsubstituted aryl or an aryl independently substituted with halo, nitro, amino, or aliphatic groups. In one embodiment, R^5 is not $-CONH_2$.

In another embodiment, R^4 is $-NH_2$; R^5 is -CN and R^6 is -H. In another embodiment, R^4 is $-NH_2$; R^5 is $-CSNH_2$ and R^6 is -H. In another embodiment, R^4 is -NH_2; R^5 is -CN and R^6 is $-NH_2$. In another embodiment, R^4 is $-NH_2$; R^5 is -CN and R^6 is a halo group. In another embodiment, the halo group is a bromo or chloro.

Some embodiments comprise a pyrrolo[2,3-*d*]pyrimidine compound having the following structural features:

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH(CH_3)-C_6H_4$ (1414);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-C_6H_4$-4-F (1429);

R^4 is NH_2; R^5 is -CN; R^6 is -H; and R^7 is $CH_2-C_6H_4$-4-Cl (1444);

R^4 is NH_2; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-C_6H_4$-4-NO_2 (1360);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is-$CH_2-C_6H_4$-3-NO_2 (1362);

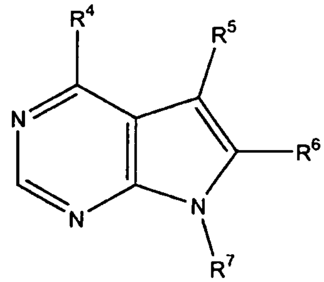
R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-(CH_2)_3-C_6H_5$ (1350);

R^4 is $-NH_2$; R^5 is $-CSNH_2$; R^6 is -H; and R^7 is $-CH_2-CH_2-C_6H_5$ (1446);

R^4 is $-NH_2$; R^5 is $-CSNH_2$; R^6 is -H; and R^7 is $-CH_2-CH_2-CH_2-C_6H_5$ (1413);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-CH_2-C_6H_5$ (1368);
R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH(CH_3)-C_6H_5$ (1451);
R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-CH_2-C_6H_5$ (1369);
R^4 is $-NHCH_3$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4-3-NO_2$ (1425);
R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4-3-NH_2$ (1455);
R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$ and R^7 is $-CH_2-C_6H_4-4-F$ (1365);
R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4-4-Cl$ (1356);
R^4 is NH_2; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4-4-Br$ (1389);
R^4 is NH_2; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2C_6H_4-4-NO_2$ (1348);
R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4-4-NH_2$ (1352);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-CH=CH-CH_2-C_6H_5$ (1372);
R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH^2$; and R^7 is $-CH_2-CH=CH-CH_2-C_6H_5$ (1329);
R^4 is -oxo; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-CH_3$ (1441);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH(CH_3)-C_6H_5$ (1363);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-F$ (1353);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-Cl$ (1355);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-3-Cl$ (1461);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_3-3,4-(Cl)_2$ (1462);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-Br$ (1373);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-NO_2$ (1374);
R^4 is $-NH-CH_3$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-CH_2-C_6H_5$ (1463);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-CH_2-C_6H_5$ (1351);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-(CH_2)_3-C_6H_5$ (1347); and
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-CH=CH-C_6H_5$ (1361).

In another embodiment of the method, one or more compounds have the following structure:



wherein:

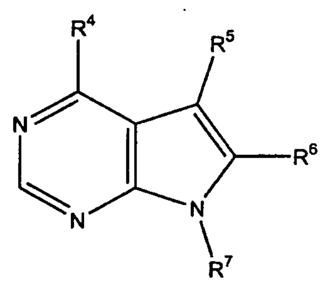
R^4 is $-NR_1R_2$ or oxo;

R^5 is $-CONR_1R_2$;

R^6 is -H, or halo, or $-NR_1R_2$;

wherein R_1 and R_2 are independently -H or an aliphatic group; and R^7 is of the formula R_3-Ar, wherein R_3 is an aliphatic group and Ar is an unsubstituted aryl or an aryl independently substituted with halo, nitro, amino, or aliphatic groups. In one embodiment, R^5 is not $-CONH_2$.

In another embodiment, one or more compounds have the following structure:



wherein:

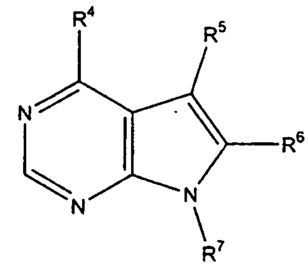
R^4 is $-NR_1R_2$ or oxo:

R^5 is -CN, or $-CSNR_1R_2$ or $-CONR_1R_2$;

R^6 is halo;

wherein R_1 and R_2 are independently -H or an aliphatic group; and R^7 is of the formula R_3-Ar, wherein R_3 is an aliphatic group and Ar is an unsubstituted aryl or an aryl independently substituted with halo, nitro, amino, or aliphatic groups. In one embodiment, R^5 is not $-CONH_2$.

In another embodiment of the method, the one or more compounds have the following structure:



wherein:

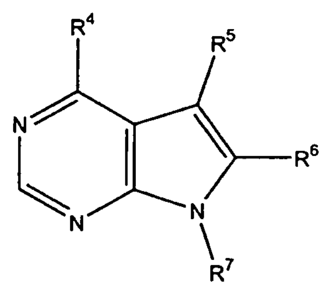
R^4 is $-NR_1R_2$ or oxo:

R^5 is -CN, or $-CSNR_1R_2$ or $-CONR_1R_2$;

R^6 is -H or halo, or $-NR_1R_2$;

wherein R_1 and R_2 are independently -H or an aliphatic group; and R^7 is of the formula R_3-Ar, wherein R_3 is an aliphatic group and Ar is an aryl independently substituted with halo, nitro, amino groups. In one embodiment, R^5 is not $-CONH_2$.

In yet another embodiment of the method, the one or more compounds have the following structure:



wherein:

R^4 is $-NR_1R_2$ or oxo:

R^5 is -CN, or $-CSNR_1R_2$ or $-CONR_1R_2$;

R^6 is -H or halo, or $-NR_1R_2$;

wherein R_1 and R_2 are independently -H or an aliphatic group; and R^7 is of the formula R_3-Ar, wherein R_3 is an aliphatic group and Ar is an unsubstituted aryl or an aryl independently substituted with halo, nitro, amino, or aliphatic groups. In one embodiment, R^5 is not $-CONH_2$.

In one embodiment, the virus is a herpes virus, or hepatitis B virus or hepatitis C virus. In another embodiment, the herpes virus is selected from the group consisting of herpes simplex virus type 1, herpes simplex virus type 2, herpesvirus type 6, varicella-zoster virus, Epstein-Barr virus, herpesvirus saimiri; equine herpesvirus-1, equine herpesvirus-2, and equine herpesvirus-3.

In another embodiment, at least one of the above compounds is used in the prevention or treatment of a viral infection. In another embodiment, at least one of the above compounds is used for the preparation of a medicament for the prevention or treatment of a viral infection. The compounds also can be used in an in vitro assay to identify other therapeutically effective compounds. The compounds can also be used in vitro to predict efficacy against a viral infection in vivo.

A further embodiment of this invention pertains to methods for treating and/or preventing a hepatitis viral infection, *e.g.*, hepatitis B and hepatitis C, comprising contacting the virus with an effective amount of an antiviral pyrrolo[2,3-*d*]pyrimidine compound of the present invention, alone or in combination with a carrier such as a pharmaceutically acceptable carrier.

The invention also includes pharmaceutically acceptable salts, prodrugs and derivatives, such as esters, of the above-described compounds. See, Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA (latest edition).

Another aspect of the invention is a method for inhibiting replication or viral infectivity in a subject by administering an effective amount of one or more of the above-described compounds to the subject.

Still another aspect of the invention is a composition for preventing or treating viral infections containing an effective amount of one or more of the above-described compounds and an acceptable carrier, *e.g.*, a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

Throughout this application, various references including but not limited to publications, patents, and published patent applications are referred to by an identifying citation. The disclosure of these references, *e.g.*, publications, patents, and published

patent specifications referenced in this application are hereby incorporated by reference into the present disclosure to more fully describe the state of the art to which this invention pertains.

The present invention provides several novel non-phosphorylatable, non-nucleoside pyrrolo[2,3-*d*]pyrimidines which are useful in the treatment or prevention of viral infections.

A. Chemical Structure

The term "nucleoside derivative" as used herein relates to pyrrolo[2,3-*d*]pyrimidine compounds which have a *modified* but *intact* furan ring at N-7 (R^7). Examples include 2',3'-dideoxy-2',3'-didehydro-β-D-ribofuranose and 2',3'-dideoxy-β-D-ribofuranose.

The term "non-nucleoside derivative" as used herein relates to pyrrolo[2,3-*d*]pyrimidine compounds which do not have a modified or intact furan ring at N-7 (R^7) but are substituted at R^7 instead with a variety of aralkyl radicals such as unsubstituted benzyls, substituted benzyls, substituted alkylphenyls, substituted alkenylphenyls, wherein the substitutions comprise a variety of groups such as halo, nitro, amino, and alkyl, among others.

The term "non-nucleoside, non-phosphorylatable derivative" as used herein relates to pyrrolo[2,3-*d*]pyrimidine compounds which do not have a modified or intact furan ring at N-7 (R^7) and are not substituted at R^7 with a radical having an available -OH (hydroxyl) group and thereby cannot be phosphorylated to an active metabolite. Examples of such substituents include various aryl, aralkyl, and oxy-hydrocarbyl radicals.

The terms "thioamide" and "thiocarboxamide" are used synonymously herein. Similarly, the terms "nitrile" and "carbonitrile" are used synonymously herein. The terms "selenamide" and "selenocarboxamide" are used synonymously herein to denote compounds having a -$CSeNH_2$ group.

The term "aryl" as used herein is generic to monocyclic aromatic radicals which may be unsubstituted, substituted, or multiply substituted. Examples of such

substituents include $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, $-OCH_3$, and $-OCH_2CH_3$. Examples of aryls include $-C_6H_5$, methylphenyl (such as $-C_6H_4$-2-CH_3, $-C_6H_4$-3-CH_3, and $-C_6H_4$-4-CH_3), dimethylphenyl (such as 2,3-dimethylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, and the like), trimethylphenyl (such as 2,4,6-trimethylphenyl and the like), methoxyphenyl (such as $-C_6H_4$-2-OCH_3, $-C_6H_4$-3-OCH_3, and $-C_6H_4$-4-OCH_3), dimethoxyphenyl (such as 2,3-dimethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, and the like), (tert-butyl)phenyl (such as $-C_6H_4$-2-$C(CH_3)_3$, $-C_6H_4$-3-$C(CH_3)_3$, and $-C_6H_4$-4-$C(CH_3)_3$), di(tert-butyl)phenyl (such as 2,3-di(tert-butyl)phenyl, 2,4-di(tert-butyl)phenyl, 2,5-di(tert-butyl)phenyl, and the like), methoxymethylphenyl (such as 4-methoxy-2-methylphenyl and the like), and tert-butylmethylphenyl (such as 4-(tert-butyl)-2-methylphenyl and the like).

The term "aralkyl" as used herein is generic to alkyl radicals having an aryl group. Examples of aralkyls include $-CH_2$-C_6H_5, methylbenzyl (such as $-CH_2$-C_6H_4-2-CH_3, $-CH_2$-C_6H_4-3-CH_3, $-CH_2$-C_6H_4-4-CH_3), dimethylbenzyl (such as 2,3-dimethylbenzyl, 2,4-dimethylbenzyl, 2,5-dimethylbenzyl, and the like), methoxybenzyl (such as $-CH_2$-C_6H_4-2-OCH_3, $-CH_2$-C_6H_4-3-OCH_3, $-CH_2$-C_6H_4-4-OCH_3), dimethoxybenzyl (such as 2,3-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,5-dimethoxybenzyl, and the like), (tert-butyl)benzyl (such as $-CH_2$-C_6H_4-2-$C(CH_3)_3$, $-CH_2$-C_6H_4-3-$C(CH_3)_3$, $-CH_2$-C_6H_4-4-$C(CH_3)_3$), di(tert-butyl)benzyl (such as 3,3-di(tert-butyl)benzyl, 2,4-di(tert-butyl)benzyl, 2,5-di(tert-butyl)benzyl, and the like), methoxymethylbenzyl (such as 4-methoxy-2-methylbenzyl and the like), tert-butylmethylbenzyl (such as 4-(tert-butyl)-2-methylbenzyl and the like), phenylethyl (such as 1-phenylethyl and 2-phenylethyl), phenylpropyl (such as 3-phenylpropyl and the like), and methoxyphenylethyl (such as 2-(2-methoxyphenyl)ethyl and the like). The substituent groups include halo, nitro, and amino groups. Optionally, the amino group could be a derivatized amino group.

Thus, the term "substituted aralkyl" includes substituted phenyl and benzyl groups, wherein the phenyl ring is substituted with one or more of the above mentioned groups.

The term "hydrocarbyl" as used herein is generic to radicals derived from hydrocarbons. The term "oxy-hydrocarbyl" as used herein is generic to hydrocarbyl radicals having at least one oxy-group. The term "oxy-group" as used herein is generic to R-O-R linkages, excluding those arising from substituents on aryl groups. Examples of oxy-groups include $-CH_2-O-CH_2-$, $-CH_2-O-C_6H_4-$, and $-CH_2-O-CH(CH_3)-$, but not $-C_6H_4-2-OCH_3$.

The term "aliphatic" as used herein is generic to linear, branched, or multiply-branched acyclic species. Examples of acyl or acyl derivatized groups include -C(=O)H, -C(=O)R, -C(=O)OH, -C(=O)OR, -C(=O)NHR, and the like.

Examples of aliphatic oxy-hydrocarbyls having 2 to 15 carbon atoms, lacking free hydroxyl groups and further lacking acyl or acyl derivatized groups include $-CH_2-O-CH_3$, $-CH_2-O-CH_2-CH_3$, $-CH_2-O-CH_2\ CH_2-CH_3$, $-CH_2-O-CH_2-CH_2-O-CH_3$, $-CH_2-O-CH_2-CH_2-O-CH_2-CH_3$, $-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_2$, $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-O-CH_2-CH_3$, $-CH_2-O-CH(CH_2-OCH_3)_2$, $-CH_2-O-CH(CH_2-OCH_2-CH_3)_2$, $-CH(CH_2-OCH_3)-O-CH(CH_2-OCH_3)_2$, and the like.

Examples of oxy-hydrocarbyls having 6 to 30 carbon atoms, at least one aryl or aralkyl group, and only one oxy-group include $-CH_2-O-C_6H_5$, $-CH_2-O-CH_2-C_6H_5$, $-CH_2-CH_2-O-C_6H_5$, $-CH_2-CH_2-O-CH_2-C_6H_5$, (methylphenyloxy)methyl (such as (4-methylphenyloxy)methyl and the like), (methylbenzyloxy)methyl (such as (4-methylbenzyloxy)methyl and the like), (methoxyphenyloxy)methyl (such as (4-methoxyphenyloxy)methyl and the like), (methoxybenzyloxy)methyl (such as (4-methoxybenzyloxy)methyl and the like), (tert-butylphenyloxy)methyl (such as (4-tert-butylphenyloxy)methyl and the like), (tert-butylbenzyloxy)methyl (such as (4-butylbenzyloxy)methyl and the like), [(methoxy)(methyl) phenyloxy]methyl (such as (4-methoxy-2-methylphenyloxy)methyl and the like), and [(methoxy)(methyl)benzyloxy]methyl (such as (4-methoxy-2-methylbenzyloxy)methyl and the like).

In a preferred embodiment, the pyrrolo[2,3-*d*]pyrimidine compound has the following structural characteristics: R^4 is $-NH_2$, R^5 is -CN, R^6 is -H, and R^7 is 4-fluorobenzyl or 4-chlorobenzyl or 4-nitrobenzyl. In another preferred embodiment, the

pyrrolo[2,3-*d*]pyrimidine compound has the following structural characteristics: R^4 is -NH_2, R^5 is -CN, R^6 is -Br or -NH_2, and R^7 is 4-fluorobenzyl or 4-chlorobenzyl or 4-nitrobenzyl.

In another preferred embodiment, the pyrrolo[2,3-*d*]pyrimidine compound has the following structural characteristics: R^4 is -NH_2, R^5 is -CN or $CSNH_2$, R^6 is -H, or bromo or NH_2 and R^7 is 2-phenylethyl. In yet another preferred embodiment, the pyrrolo[2,3-*d*]pyrimidine compound has the following structural characteristics: R^4 is -NH_2, R^5 is -CN or -$CSNH_2$, R^6 is -H or -NH_2, and R^7 is 3-phenylpropyl.

Compounds of the invention include the following: 4-amino-7-((2-phenyl)eth-2-yl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-7-(4-fluorobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-7-(4-chlorobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-7-(4-nitrobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-7-(3-nitrobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-7-benzyl-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide; 4-amino-7-((2-phenyl)-eth-2-yl)-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide; 4-amino-7-(2-methylbenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide; 4-amino-7-(3-methylbenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide; 4-amino-7-(4-methylbenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide; 4-amino-7-(4-t-butylbenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide; 4-amino-7-(4-methoxybenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide; 4-amino-7-(4-fluorobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide; 4-amino-7-(4-nitrobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide; 4-amino-7-(3-nitrobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide; 4-oxo-6-bromo-7-(4-methylbenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-6-bromo-7((2-phenyl)eth-2-yl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-6-bromo-7-(4-flurobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-6-bromo-7-(4-chlorobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide; 4-amino-6-bromo-7-(4-chlorobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-6-bromo-7-(3-chlorobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-6-bromo-7-(3,4-dichlorobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-6-bromo-7-(4-bromobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-6-bromo-7-(4-nitrobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-6-bromo-7-(3-

nitrobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-6-bromo-7-(4-methylbenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide; 4,6-diamino-7-((2-phenyl)eth-2-yl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4,6-diamino-7-(4-fluorobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4,6-diamino-7-(4-chlorobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4,6-diamino-7-(4-bromobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4,6-diamino-7-(4-nitrobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4,6-diamino-7-(4-aminobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4,6-diamino-7-(3-nitrobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4,6-diamino-7-(3-aminobenzyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-7-(2-phenyl)ethyl-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-7-(2-phenyl)ethyl-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide; 4-amino-7-(2-phenyl)ethyl-pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide; 4-methylamino-6-bromo-7-(2-phenyl)ethyl-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-6-bromo-7-(2-phenyl)ethyl-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-6-bromo-7-(2-phenyl)ethyl-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide; 4,6-*d*iamino-7-(2-phenyl)ethyl-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-7-(3-phenyl)propyl-pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide; 4-amino-7-(3-phenyl)propyl-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide; 4-amino-7-(3-phenyl)propyl-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-6-bromo-7-(3-phenyl)propyl-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4,6-diamino-7-(3-phenyl)propyl-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-6-bromo-7-(3-phenyl)prop-2-enyl-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-7-(3-phenyl)prop-2-enyl-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; and 4,6-diamino-7-(3-phenyl)prop-2-enyl-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile.

B. Formulation and Use of Compounds

The compounds of the present invention exhibit superior antiviral activity and acceptable cytotoxicity for use as therapeutic agents for preventing or treating viral infections. In particular, it has been found that these compounds are effective against HCMV and HSV-1 viruses.

Prior studies indicated that certain 4-amino-7-[(2-methoxyethoxy)methyl] pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (a compound disclosed as compound 5b in U.S. Patent No. 5,543,413) inhibited HCMV and HSV-1 viral replication by a mechanism other than through inhibition of DNA synthesis because the inhibition was shown to occur through a mechanism early in the replication cycle. Accordingly, it is expected that compounds of the present invention can be effective against RNA viruses such as hepatitis B and hepatitis C as well.

A partial list of mammalian viruses contemplated to be treatable with the compounds of the present invention includes: herpes simplex virus types 1 and 2; human cytomegalovirus; human immunodeficiency virus; human herpesvirus 6 (HHV6); varicella-zoster virus; Epstein-Barr virus (EBV); herpesvirus simiae; equine herpesvirus-1, 2 and 3; neurolymphomatosis (Marek's disease); influenza viruses A, B and C; parainfluenza viruses-1, 2, 3 and 4; adenovirus; reovirus; respiratory syncytial virus; rhinovirus; coxsackie virus; echo virus; rubeola virus; hepatitis viruses of the types B and C; and papovavirus.

Members of the herpes virus family (Herpesviridae) share a common virion architecture. A typical herpes virion consists of: (a) a core containing a linear, double-stranded DNA; (b) an icosahedral capsid, approximately 100-120 nm in diameter, containing 162 capsomeres; (c) an amorphous, sometimes asymmetric material that surrounds the capsid, designated as the tegument; and (d) an envelope containing viral glycoprotein spikes on its surface.

Major examples of human pathogens of the herpes viruses family include herpes simplex viruses (HSV) 1, 2, and cercopithecine herpesvirus 1 (B-virus); varicella-zoster (which causes chickenpox and shingles); Epstein-Barr virus (EBV, which causes mononucleosis); lymphocryptovirus; human herpesvirus 6 (HHV6); human herpesvirus 7 (HHV7) and kaposi-associated herpesvirus (KHV); or human herpesvirus 8 (HHV8). Human cytomegalovirus (HCMV), also a human herpesvirus, is a leading opportunistic pathogen among immunosuppressed individuals. See, Alford, C.A.; Britt, W.J., in: *The Human Herpesviruses*, Roizman, B. et al. (Eds.), Raven Press, New York, 1993,

pp. 227-255. In neonates, see Alford, C.A. et al., *Rev. Infect. Dis.* 1990, *12*:s793-s804 and Gallant, J.E. *et al.*, *J. Infect. Dis.* 1992, *166*, 1223-1227.

Animal pathogens include infectious bovine rhinotracheitis virus, bovine mammillitis virus, cercopithecine herpesvirus 1 (B-virus), which are all simplexviruses; pseudorabies virus (PRV, of swine), equine rhinopneumonitis and coital exanthema viruses (varicella viruses); baboon herpesvirus, pongine (chimpanzee) herpesvirus (lymphocryptovirus); Marek's disease virus (of fowl), turkey herpesvirus; herpesvirus ateles and herpes virus saimiri (rhadinovirus); among others. For reviews see, Murphy *et al.*, Virus Taxonomy, in Fields *et al.* (eds.) Fundamental Virology, 1991, Raven Press, New York, pp. 9-36; Watson *et al.*, Molecular Biology of the Gene, Fourth Edition, 1987, Benjamin/Cummings Publ. Co., Menlo Park, CA, pp. 904, 933.

Herpesvirus genomes, which are generally 120 to 230 kb long, encode 50 to 200 different proteins. These include a large array of enzymes involved in nucleic acid metabolism (*e.g.*, thymidine kinase, thymidylate synthetase, dUTPase, ribonucleotide reductase, etc.), and DNA synthesis (*e.g.*, DNA polymerase, helicase, primase).

Some herpesviruses such as HSV-1 and HSV-2 have a wide host-cell range, multiply efficiently and rapidly destroy infected cells. Others (*e.g.*, EBV, HHV6) have a narrow host-cell range or, in the case of HCMV, replicate slowly. For reviews see, Roizman *et al.*, Herpes Simplex Viruses and Their Replication, in Fields *et al.* (eds.) Fundamental Virology, 1991, Raven Press, New York, pp. 849-895.

Herpesviruses replicate in the cell nucleus, wherein the nucleolus is displaced, disaggregated and then fragmented, and host chromosomes are marginated, which may lead to chromosome breakage. Host protein synthesis declines very rapidly (for most herpesviruses, but not HCMV), host ribosomal RNA synthesis is reduced, and glycosylation of host proteins ceases. Production of progeny is invariably accompanied by the irreversible destruction of the infected cell. For reviews see, *et al.*, Herpes Simplex Viruses and Their Replication, in Fields *et al.* (eds.) Fundamental Virology, 1991, Raven Press, New York, pp. 849-895.

A variety of disease symptoms and a complex clinical course are caused by herpesviruses. In the case of a first infection in an adult human, the symptoms may be

very severe. Herpes viruses can cause recurrent infections, and the disability associated with these recurrences is a significant health problem. The most frequent manifestations of recurrent herpetic disease states were disclosed to involve the orofacial and genital regions and recurrent herpetic keratitis was characterized as a leading cause of blindness in the United States. Herpetic genital infections with a high incidence of subsequent recurrent episodes were noted as being recognized more frequently and being associated with significant morbidity. See, Cohen *et al.*, U.S. Patent No. 4,709,011, issued Nov. 24, 1987.

In the case of EBV and HCMV, acute hepatitis is frequently associated with infectious mononucleosis. Mononuclear cells are the major candidate as cells involved in the latent state of HCMV infection, and infectious mononucleosis may follow blood transfusions from seropositive to seronegative individuals. Seronegative individuals may also become infected via transplantation of cells or organs from seropositive donors. For reviews see, Ahmed *et al.*, Viral Persistence, in Fields *et al.* (eds.) Fundamental Virology, 1991, Raven Press, New York, pp. 241-265; Stinski, Cytomegalovirus and Its Replication, in Fields *et al.* (eds.) Fundamental Virology, 1991, Raven Press, New York, pp. 929-950.

A herpesvirus of economic importance in the cattle industry is Bovine Herpesvirus-1 (BHV-1), which has been associated with a variety of clinical disease manifestations, including rhinotracheitis, vulvovaginitis, abortions, conjunctivitis, encephalitis and generalized systemic infections. Gibbs *et al.*, 1977 Bovine Herpesviruses. I: Bovine herpesvirus-1. *Vet. Bull.* (*London*) 47:317-343.

The herpesvirus Pseudorabies virus (PRV), also called Aujeszky's disease virus (ADV), is a disease of all domestic animals, with the exception of the horse, and causes severe damage, especially among pigs and cattle. The pig is the natural host of ADV. Animals are infected via the nasal route and, after a primary virus multiplication in the mucous membranes of upper respiratory and digestive tracts, the virus spreads via nerves to the brain. The infection proceeds acutely to sub-clinically, which is mainly dependent on the virulence of the virus and the age of the pigs. PRV, just as other

herpesviruses induce latent infections, namely in the nerve tissues. Berns *et al.*, U.S. Patent No. 4,680,176, issued July 14, 1987.

Currently, only three drugs have been FDA-approved for the treatment of HCMV infections: gancyclovir (see Crumpacker, C.S., Ganciclovir. *New England J. Med.* 1966, *335*, 721-729), foscarnet (see Chrisp, P. and Clissold, S.P., Foscarnet. A Review of its Antiviral Activity, Pharmacokinetic Properties and Therapeutic Use in Immunocompromised Patients with Cytomegalovirus Retinitis. *Drugs* 1991, *41*:104-129), and cidofivir (see Hitchcock, M.J. *et al., Antiviral Chem.& Chemother.* 1996, *7*:115-127; Lalezari, J.P. *et al., J. Infect. Dis.* 1995, *171*:788-796). All of these drugs can lead to side-effects such as renal dysfunction (foscarnet and cidofivir) and granulocytopenia (ganciclovir). Additionally, potential drug resistance and poor oral bioavailability create a need for more potent and selective drugs (see Field, A.K. and Biron, K.K., "The End of Innocence Revisited: Resistance of Herpesviruses to Antiviral Drugs" *Clin. Microbiol. Rev.* 1994, *7*:1-13).

The hepatitis B virus (HBV) infects hepatocytes and causes acute and chronic liver disease and hepatocellular carcinoma. Infection is typically via contaminated blood or body fluids, and thus HBV infection is prevalent among intravenous drug abusers, homosexuals, and in countries with less developed health care systems where the risk of exposure to contaminated blood products is high. Approximately 90-95% of infected individuals are able to resolve their infection, while the remaining 5-10% develop chronic hepatitis and lapse into a carrier state, with the possibility of later developing liver cirrhosis and/or hepatocellular carcinoma. It has recently been estimated that throughout the world there are approximately 250 million people who are chronic carriers of HBV.

The pathogenic mechanisms responsible for liver cell injury in HBV infection are not well understood, although it is believed that the virus is not directly cytopathic. Since HBV does not readily infect human cells in vitro, however, the virus has been extremely difficult to study. Consequently, as yet there is no effective treatment for an established HBV infection.

Hepatitis C, which is neither hepatitis A nor hepatitis B, forms 95 to 100% of post-transfusion hepatitis and 40 to 50% of sporadic hepatitis and easily becomes chronic, further changing at high rates to cancer of the liver via chronic hepatitis or hepatic cirrhosis. Recently, hepatitis C virus (HCV) was identified, and it has been demonstrated that most of the hepatitis previously known as non-hepatitis A or non-hepatitis B are caused by this hepatitis C virus.

Although interferon is known as an agent having inhibitory effects on the proliferation of hepatitis C virus, it is noted that interferon has a low rate of effectiveness (as little as 30 to 40%), with a 60 to 70% recrudescence after discontinuance of the dosage thereof, thus creating the appearance of influenza-like symptoms, such as pyrexia, headache and vomiting, and of diverse side effects such leukopenia, at the high rates. Accordingly, there exists currently no effective treatment or preventive with an acceptable efficacy and toxicity profile.

In this regard it will also be appreciated that "treatment" in accordance with the present invention encompasses the treatment of viral infections, as well as prophylactic treatment of patients who are at risk for viral infection, *e.g.*, immunocompromised patients, such as bone marrow transplant patients.

The term "pharmaceutically acceptable salt, prodrug or derivative," as used herein, relates to any pharmaceutically acceptable salt, ester, ether, salt of an ester, solvate, such as ethanolate, or other derivative of a compound of the present invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an active metabolite or residue thereof. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (*e.g.*, by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (*e.g.*, the brain or lymphatic system).

Salts of the compounds of the present invention may be derived from inorganic or organic acids and bases. Examples of acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic,

succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. Examples of bases include alkali metal (*e.g.*, sodium) hydroxides, alkaline earth metal (*e.g.*, magnesium) hydroxides, ammonia, and compounds of formula NW_4^-, wherein W is C_{1-4} alkyl.

Examples of salts include: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, flucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylproprionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate. Other examples of salts include anions of the compounds of the present invention compounded with a suitable cation such as Na^+, NH_4^+, and NW_4^+ (wherein W is a C_{1-4} alkyl group).

For therapeutic use, salts of the compounds of the present invention will be pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

Esters of the compounds of the present invention include carboxylic acid esters (*i.e.*, -O-C(=O)R) obtained by esterification of the 2'-, 3'- and/or 5'-hydroxy groups, in which R is selected from (1) straight or branched chain alkyl (for example, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted by, for example, halogen, C_{1-4} alkyl, or C_{1-4} alkoxy or amino); (2) sulfonate esters, such as alkylsulfonyl (for example, methanesulfonyl) or aralkylsulfonyl; (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4)

phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di-(C_{6-24})acyl glycerol. In such esters, unless otherwise specified, any alkyl moiety present advantageously contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms. Any cycloalkyl moiety present in such esters advantageously contains from 3 to 6 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group. Examples of prodrug derivatives of the present invention include, for example, those with chemically protected hydroxyl groups (*e.g.*, with O-acetyl groups).

Ethers of the compounds of the present invention include methyl, ethyl, propyl, butyl, isobutyl, and sec-butyl ethers.

One aspect of the present invention pertains to methods for inhibiting viral replication and/or propagation *in vitro*, *ex vivo* or *in vivo*, by contacting the virus with an effective amount of a compound effective to inhibit viral replication and/or propagation. When the contacting is done *in vitro*, the compounds are useful to screen for other antiviral compounds that may be used independently or in combination with the compounds disclosed herein. The compounds also are useful for treating and/or preventing a viral infection by administering to an infected host a therapeutically effective amount of pyrrolo[2,3-*d*]pyrimidine compound of the present invention. In one embodiment, such methods include administering to an infected host a composition of a pharmaceutically acceptable carrier and a therapeutically effective amount of an antiviral pyrrolo[2,3-*d*]pyrimidine compound of the present invention.

The term "effective amount" is to include a prophylactically effective amount and refers to an amount effective in treating or preventing a viral infection in a patient either as monotherapy or in combination with other agents. The term "treating" as used herein refers to the alleviation of symptoms of a particular disorder in a patient or the improvement of an ascertainable measurement associated with a particular disorder or a reduction in viral titer in the host. One of the skill in the art can determine when a host has been "treated" by noting a reduction in viral load or an alleviation in symptoms associated with viral infection. The term "prophylactically effective amount" refers to

an amount effective in preventing viral infection in a host. As used herein, the term "host" refers to a mammal, such as a mouse, bovine, rat or a human patient.

The term "biologically acceptable carrier" refers to a carrier or adjuvant that may be administered to a host or patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is non-toxic, when administered in does sufficient to deliver an effective amount of the antiviral compound. Examples of suitable carriers include liquid phase carriers, such as sterile or aqueous solutions, as well as those described below.

As shown below, the compounds of this invention are potent antiviral drugs and as such, when combined with carriers, provide compositions for inhibiting viral reproduction and proliferation *in vitro, ex vivo* or *in vivo*. However, it should be understood, although not explicitly stated, that other virus, such as HHV-6 and HIV can be inhibited by the compounds of this invention. Methods of determining efficacy against these viruses are provided below. In addition, RNA virus can be inhibited by the compounds of this invention.

The compounds of this invention also can be employed in combination with other therapeutic agents for the inhibition of the replication or propagation of the above virus and associated conditions. Combination therapies, according to the present invention, comprise the administration of at least one compound of the present invention, and at least one other pharmaceutically active ingredient. The active ingredient(s) and pharmaceutically active agents may be administered simultaneously in either the same or different pharmaceutical formulations, or sequentially in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s), and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. Preferably the combination therapy involves the administration of one compound according to the invention and one of the agents mentioned herein below. The term "operative combination" is intended to include any chemically compatible combination of a compound of the present invention with other compounds of the present invention or other compounds outside the present invention

(such as ganciclovir, AZT, and foscarnet), as long as the combination does not eliminate the antiviral activity of the compound of the present invention.

Examples of other active ingredients include agents that are effective for the treatment of viral infections or associated conditions and include (1-alpha, 2-beta, 3-alpha)-9-[2,3-bis(hydroxymethyl)cyclobutyl]guanine [(-)BHCG, SQ-34514], oxetanocin-G(3,4-bis-(hydroxymethyl)-2-oxetanosyl]guanine), acyclic nucleosides (*e.g.*, acyclovir, valaciclovir, famciclovir, ganciclovir, penciclovir), acyclic nucleoside phosphonates (*e.g.*, (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC), ribonucleotide reductase inhibitors such as 2-acetylpyridine 5-[(2-chloroanilino)thiocarbonyl]thiocarbonohydrazone, 3'-azido-3'-deoxythymidine, other 2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, 2',3'-didehydrothymidine, protease inhibitors such as ritonovir, indinavir, 141W94, nelfinavir, sanquinavir, and 3S-[3R*(1S*,2R*)]-[3-[[(4-aminophenyl)sulphonyl](2-methylpropyl)-amino]-2-hydroxy-1-phenylmethyl)propyl]carbamic acid, tetrahydro-3-furanyl ester (141W94), oxathiolane nucleoside analogues such as (-)-*cis*-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-cytosine (lamivudine) or *cis*-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC), 3'-deoxy-3'-fluorothymidine, 5-chloro-2',3'-dideoxy3'-fluorouridine, (-)-cis-4-[2-amino-6(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol, ribavirin, 9-[4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (H2G), tat inhibitors such as 7-chloro-5-(2-pyrryl)-3H-1,4-benzodiazepin-2-(*H*)one (Ro5-3335), 7-chloro-1,3-dihydro-5-(1H-pyrrol-2-yl)-3H-1,4-benzodiazepin-2-(*H*)one (Ro5-3335), 7-chloro-1,3-dihydro-5-(2-pyrryl)-3H-1,4-benzodiazepin-2-amine (Ro24-7429), interferons such as (α-interferon, renal excretion inhibitors such as probenecid, nucleoside transport inhibitors such as dipyridamole; pentoxifylline, N-acetylcysteine (NAC), Procysteine, (α-trichosanthin, phosphonoformic acid, as well as immunomodulators such as interleukin II or thymosin, granulocyte macrophage colony stimulating factors, erythropoetin, soluble CD_4 and genetically engineered derivatives thereof, or non-nucleoside reverse transcriptase inhibitors such as nevirapine (BI-RG-587), loviride (α-APA) and delavuridine (BHAP), and phosphonoformic acid.

The compounds of the invention could also be used to treat HCMV and HSV-1 infections in AIDS patients already receiving the antiviral drug zidovudine (AZT) and/or 3TC. Combination therapies with AZT may provide the advantage of less toxicity over the combination of ganciclovir with AZT. The combination of the compounds of this invention with AZT may produce less cytotoxicity (*i.e.*, antagonism) in cultured human cells than either agent used alone. In contrast, the combination of ganciclovir with AZT may produce greater cytotoxicity in human cells than the use of either of those drugs alone.

For the purposes of this invention, a "cell" is intended to include, but not be limited to, a mammalian cell, *e.g.*, a mouse cell, a bovine cell, a rat cell, a woodchuck cell, a simian cell, or a human cell. Viruses which are effectively treated by the compounds, compositions and methods of this invention include DNA and RNA viruses, particularly herpes-type viruses. Examples of herpes-type viruses, or herpesviridae, are herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), human cytomegalovirus (HCMV), human herpes virus 6 (HHV-6), human herpes virus 7 (HHV-7), and human herpes virus 8 (HHV-8). The compounds of the present invention are particularly useful in the treatment of HCMV and HSV-1 infections, and associated pathologies such as restenosis. They also are suitably used in the treatment of hepatitis associated disorders such as hepatocellular carcinoma (See, U.S. Patent No. 5,679,342).

Effective amounts are easily determined by those of skill in the art and will vary with the cell, virus being effected, and the purpose of the treatment. For example, when utilizing the drug in cell culture, it is important that the amount of drug not be cytotoxic to the cells.

"Suitable conditions" include *in vitro*, *ex vivo* or *in vivo*. When the method is practiced *in vitro*, contacting may be effected by incubating the cells with an effective antiviral amount of the compound, effective to inhibit viral reproduction and proliferation in the cell or culture of cells. The compound can be added directly to the culture media or combined with a carrier prior to addition to the cells. *In vitro*, the method is particularly useful for inhibiting viral reproduction, proliferation and

therefore infection in laboratory cell cultures. *Ex vivo*, the compounds are useful to inhibit viral reproduction and proliferation in blood and plasma prior to reintroduction into a patient.

The use of the compounds and methods *in vitro* also provides a powerful bioassay to screen for novel drugs or compounds which provide similar or enhanced antiviral activity. Using the methods set forth below, the drug to be tested is assayed under the same conditions as a compound of this invention. Antiviral and cytotoxicity of the test drug can then be compared to a compound of this inventive group.

Although the compounds are shown below to be particularly effective against HCMV and HSV-1, it is within the scope of this invention that other viruses are effectively treated with the compounds of this invention by use of methods described herein, and others well known to those of skill in the art. Other viruses that can be treated as defined herein, and within the scope of the present invention, include all members of the herpes family, and human immunodeficiency virus (HIV) and hepatitis viruses, for example, hepatitis B virus (HBV). Methods of determining the efficacy of any of the compounds of this invention against HBV are well known in the art; see for example, the methods shown in U.S. Patent No. 5,399,580 to Daluge.

An additional member of the hepatitis virus family that can be treated as defined herein is hepatitis C virus (HCV). U.S. Patent No. 5,679,342, issued to Houghton *et al.* describes in detail, methods for employing an extracorporeal cell system infected with HCV, to screen for the compounds most active against HCV. In brief, the method comprises: (a) providing a composition containing the compound of this invention to be tested; (b) providing an extracorporeal cell system capable of being infected by HCV; (c) providing a biological sample containing infective HCV; (d) incubating the compositions of (a) and (c) with the cell system of (b) under conditions that would, in the absence of (a), allow infection of HCV in the cell system; and (e) detecting inhibition of viral infection after incubation. Preferred cell systems as disclosed in U.S. Patent No. 5,679,342, include hepatocytes, macrophages, more preferably Kupffer macrophages, and B lymphocytes. Cell lines derived from organs of hepatocytic origin also are suitable for use in the assay described above. One can also use the above noted

assay to test for the inhibition of viral replication by incubating the compositions of (a) and (b) under conditions that would, in the absence of (a), allow replication of HCV in the cell line and then detecting inhibition of viral replication after incubation.

Another method well known in the art for testing the antiviral activity of compounds against HCV is the helicase inhibition assay described, for example, in Lain *et al.*, (1991) *Nucleic Acids Res.* 69:1720-1726 and Kim *et al.*, (1995) *Biochem. Biophys. Res. Comm.* 160-166.

When the method is practiced *in vivo* in a subject, such as a human patient, the compound can be added to a pharmaceutically acceptable carrier and systemically or topically administered to the subject, such as a human patient or a mammal such as a mouse, a rat, a woodchuck, or a simian.

It should be understood that by preventing or inhibiting viral proliferation, infection and replication in a subject or individual, the compositions and methods of this invention also provide methods for treating, preventing or ameliorating the symptoms or disorders associated with the viral infection, such as inclusion disease, blindness, mononucleosis, restenosis (HCMV); chickenpox, shingles (varicella-zoster virus); infectious mononucleosis, glandular, fever, and Burkitt's lymphoma (Esptein-Barr virus); cold sores (herpes simplex virus 1); genital herpes (herpes simplex virus 2); roseola infantum (human herpes virus 6, human herpes virus 7); kaposi sarcoma (human herpes virus 8). Thus, this invention also provides methods of ameliorating, preventing, or treating disorders or symptoms associated with viral infection, *e.g.*, HCMV, HSV-1 and herpes viral infection, *e.g.*, restenosis, opportunistic infections (such as retinal infections, gastrointestinal infections, pneumonia, CNS infections or liver damage) and *in utero* infections, by administering to the subject an effective amount of a compound of this invention under suitable conditions such that the disorder or symptom is ameliorated, prevented, or treated.

Restenosis is the narrowing of the blood vessels which can occur after injury to the vessel wall, for example, injury caused by balloon angioplasty or other surgical techniques, and is characterized by excess proliferation of smooth muscle cells in the walls of the blood vessel treated. Restenosis following angioplasty (RFA) occurs in

patients who have been treated for coronary artery disease by balloon angioplasty. It is thought that in many patients suffering from RFA, viral infection, particularly by CMV and/or HHV-6, of the patient plays a pivotal role in the proliferation of the smooth muscle cells in the coronary vessel treated. Thus, the compounds of this invention can be used in methods to prevent or treat restenosis in a susceptible subject or patient.

Administration *in vivo* can be effected in one dose, continuously or intermittently throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the composition used for therapy, the target virus, the purpose of the therapy, the target cell being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician. Suitable dosage formulations and methods of administering the compounds can be found below.

The compounds of the present invention all exhibit antiviral activity against HCMV, herpes viral infection and HSV-1, many with acceptable cytotoxicity. It will be appreciated that compounds of the present invention which exhibit relatively high antiviral activity versus cytotoxicity, *i.e.*, good selectivity, are preferred. It will also be appreciated that antiviral treatment in accordance with the present invention encompasses the treatment of viral infections, as well as prophylactic treatment which may be desired in certain situations, *e.g.*, in immunocompromised patients, such as bone marrow and organ transplant patients as well as patients harboring HIV who are particularly susceptible to HCMV, herpesvirus, or HSV-1 infection.

The compounds and compositions of the present invention can be used in the manufacture of medicaments and in antiviral treatment of humans and other animals, by administration in accordance with conventional procedures, such as an active ingredient in pharmaceutical compositions. Techniques and formulations may be found, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA (latest edition).

In general, a suitable dose for each of the above-named viral infections, is in the range of about 0.1 to about 250 mg per kilogram body weight of the recipient per day,

preferably in the range of about 1 to 100 mg per kilogram body weight per day, and most preferably in the range of about 5 to about 20 mg per kilogram body weight per day. Unless otherwise indicated, all weights of active ingredients are calculated as the parent compound of the formula of the present invention; for salts or esters thereof, the weights would be increased proportionately. The desired dose is preferably presented as two, three, four, five, six or more sub-doses, administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing about 10 to about 1000 mg, preferably about 20 to about 500 mg, and most preferably about 100 to about 400 mg of active ingredient per unit dosage form. It will be appreciated that appropriate dosages of the compounds and compositions of the invention may depend on the type and severity of the viral infection and can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects of the antiviral treatments of the present invention.

Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.25 to about 100 μM, preferably about 0.5 to about 70 μM, most preferably about 1 to about 50 μM. This may be achieved, for example, by the intravenous injection of about 0.1 to about 5% solution of the active ingredient, optionally in saline, or orally administered, for example, as a tablet, capsule or syrup containing about 0.1 to about 250 mg per kilogram of the active ingredient. Desirable blood levels may be maintained by a continuous infusion to provide about 0.01 to about 5.0 mg/kg/hour or by intermittent infusions containing about 0.4 to about 15 mg per kilogram of the active ingredient.

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation comprising at least one active ingredient, as defined above, together with one or more pharmaceutically acceptable carriers, such as diluents or excipients which may include, for example, fillers, extenders, wetting agents, disintegrants, surface-active agents, or lubricants, depending on the nature and mode of administration and the dosage forms. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the

formulation and not injurious to the patient. The pharmaceutical formulation may optionally include other therapeutic agents.

Formulations include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vagina, parenteral (including subcutaneous, intramuscular, intravenous and intradermal) and pulmonary administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with liquid carriers, or finely divided solid carriers, or both, and then if necessary shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (*e.g.*, povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (*e.g.*, sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or

tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical compositions for topical administration according to the present invention may be formulated as an ointment, cream, suspension, lotion, powder, solution, paste, gel, spray, aerosol or oil. Alternatively, a formulation may comprise a patch or a dressing, such as a bandage or adhesive plaster impregnated with active ingredients, and optionally one or more excipients or diluents.

The active compound can be provided in the form of pharmaceutically acceptable salts. As used herein, the term pharmaceutically acceptable salts or complexes, refers to salts or complexes of the nucleosides that retain the desired biological activity of the parent compound and exhibit minimal, if any, undesired toxicological effects. Nonlimiting examples of such salts are (a) acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acids, naphthalenedisulfonic acids, and polygalacturonic acid; (b) base addition salts formed with cations such as sodium, potassium, zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel, cadmium, sodium, potassium, and the like, or with an organic cation formed from N,N-dibenzylethylenediamine, ammonium, or ethylenediamine; or (c) combinations of (a) and (b); *e.g.*, a zinc tannate salt or the like.

The active compound, or pharmaceutically acceptable derivative or salt thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, anti-inflammatories, or other antivirals, including anti-HBV or anti-HIV agents.

For infections of the eye or other external tissues, *e.g.*, mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient in an amount of, for example, about 0.075 to about 20% w/w, preferably

about 0.2 to about 15% w/w and most preferably about 0.5 to about 10% w/w. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, *i.e.*, an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil, or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s), make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base, which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulphate.

The choice of suitable oils or fats for the formation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus the cream should preferably be a non-greasy, non-staining and washable product, with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate,

butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulation in a concentration of about 0.5 to about 20%, advantageously at about 0.5 to about 10%, and particularly about 1.5% w/w.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

Formulations suitable for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of about 20 to about 500 microns, which is administered in the manner in which snuff is taken, *i.e.*, by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid for administration, for example, a nasal spray or a nasal drops, include aqueous or oily solutions of the active ingredient.

Formulations suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions, which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried

(lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, water or injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or unit, daily subdose, as herein above-recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art, having regard to the type of formulation in question, for example, those suitable or oral administration may include such further agents as sweeteners, thickeners and flavoring agents.

Compounds of the formula of the present invention may also be presented for use in the form of veterinary formulations, which may be prepared, for example, by methods that are conventional in the art.

C. Synthesis of Compounds

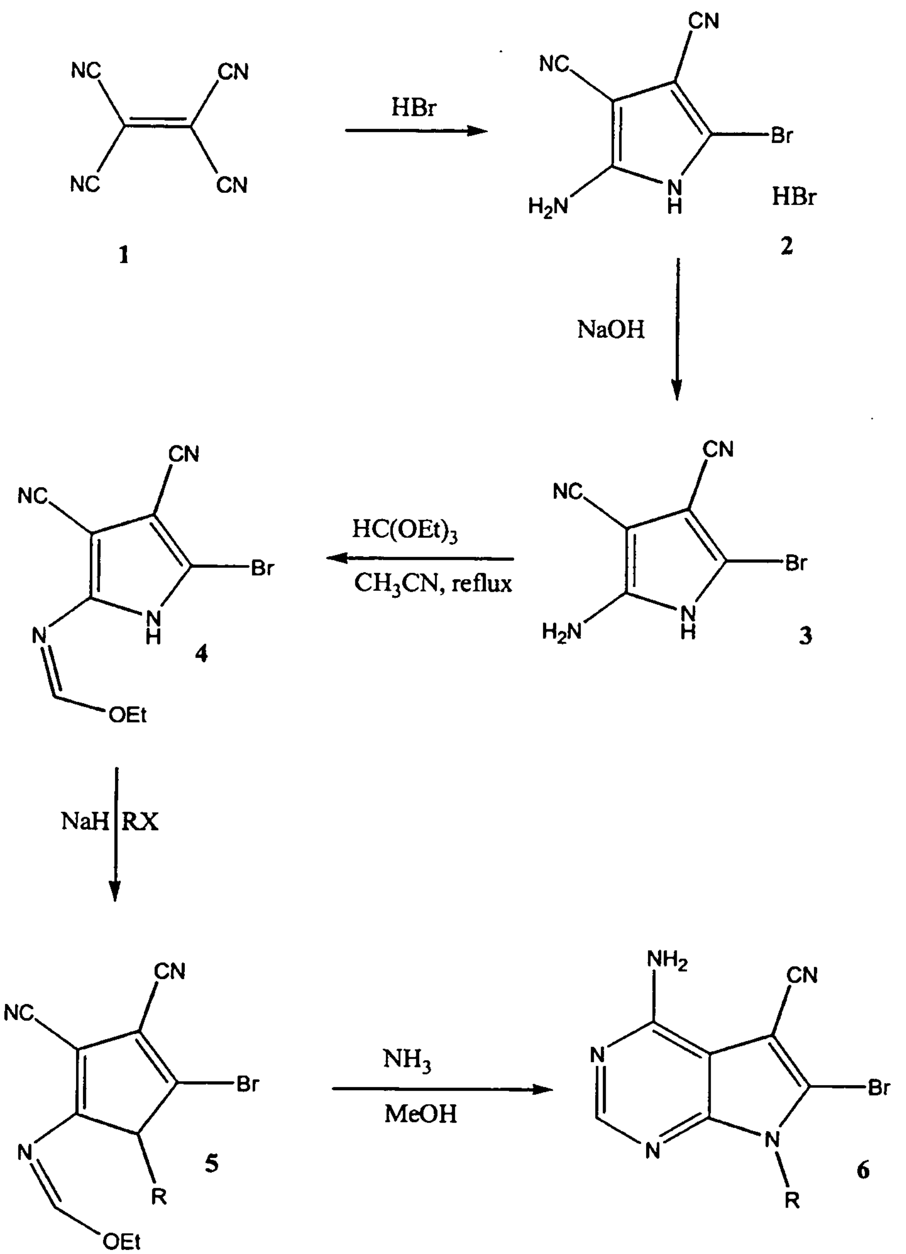
The following equipment, solvents, chemicals, and analytical methodology were employed in preparing the compounds of the present invention. ^1H NMR spectra were recorded on a Bruker 300 or 500 MHz spectrometer with DMSO-D_6 and $CDCl_3$, as solvents. Chemical shifts were reported in δ values (ppm) relative to the internal standard tetramethylsilane (TMS). Elemental analyses were performed by Analytical Services, Department of Chemistry, The University of Michigan. Melting points were taken on a Laboratory Device capillary melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was run on silica gel 60F-254 plates (Analtech, Inc.). Detection of components on TLC was made by UV light absorption at 254 nm. Silica gel (230-400 mesh) that was used for flash chromatography was obtained from Lagand Chemical Company, Inc. Evaporations were carried out on a rotary evaporator under reduced pressure (water aspirator) with the varying bath temperatures. Dry solvents

were obtained from stills. THF was dried over sodium, and acetonitrile was dried over calcium hydride. Yields were not optimized.

1. General Synthetic Methods

The compounds of the present invention can be synthesized in accordance with the procedures described below.

a. General procedure to prepare 7-alkylated-4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidines **(6)** The general procedure to prepare 7-alkylated-4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidines**(6)** from tetracyanoethylene is illustrated in Scheme 1 as below.



6a, R=4-Fluorobenzyl
6b, R=4-Trifluoromethylbenzyl
6c, R=2-Trifluoromethylbenzyl
6d, R=4-Nitrophenethyl
6e, R=4-Chlorophenethyl

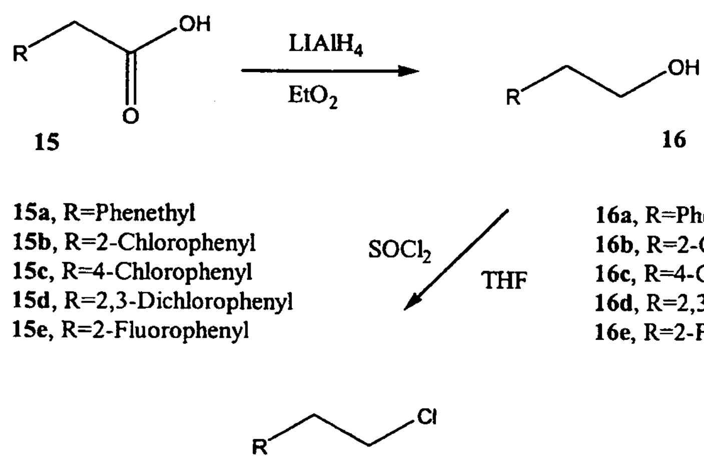
Scheme 1

Tetracyanoethylene (**1**) is reacted with HBr followed by treatment with a base such as NaOH to produce 2-amino-5-bromo-3,4-dicyanopyrrole (**3**). Treatment of **3**

with triethyl orthoformate followed by the addition of sodium hydride and one equivalent of the appropriate alkylating agent, with a catalytic amount of tetrabutylammonium iodide, gives the intermediate **(5)**. The synthetic route is dependent upon correctly placing the alkyl substituents on the N7 position.

Alkylation of **5** before cyclization controls the regiochemistry. Reaction of **5** with methanolic ammonia affords the 7-alkylated-4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidines **(6)**. Thus, by selecting the appropriate alkyl substituent, the desired 7-alkylated-4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidines can be prepared.

A variety of alkylating groups **(17a-e)** was needed in order to synthesize new phenethyl derivatives of the pyrrolo[2,3-*d*]pyrimidine. These alkylating agent can be prepared according to Scheme 2.



15 **16**

15a, R=Phenethyl
15b, R=2-Chlorophenyl
15c, R=4-Chlorophenyl
15d, R=2,3-Dichlorophenyl
15e, R=2-Fluorophenyl

16a, R=Phenethyl
16b, R=2-Chlorophenyl
16c, R=4-Chlorophenyl
16d, R=2,3-Dichlorophenyl
16e, R=2-Fluorophenyl

17

17a, R=Phenethyl
17b, R=2-Chlorophenyl
17c, R=4-Chlorophenyl
17d, R=2,3-Dichlorophenyl
17e, R=2-Fluorophenyl

Scheme 2

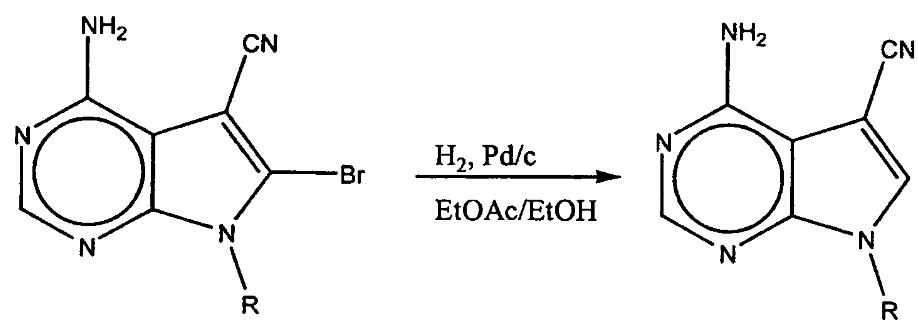
Using the substituted carboxylic acids **(15a-e)** as precursors, the corresponding alcohols **(16a-e)** could be synthesized in high yields by the action of lithium aluminum

hydride. Treatment of **16a-e** with thionyl chloride, using lithium chloride to aid in substitution, produces the chlorides **(17a-e)**.

The majority of the phenethyl halide alkylating agents, through multiple trials, gave poor yields. A change in solvent and temperature did not appreciably affect the reaction rates or yields. Accordingly, different leaving groups, in place of the halides, need to be tried to create the desired products in more efficient yields.

b. General procedure to prepare 7-alkylated-4-amino-5-cyanopyrrolo[2,3-*d*]pyrimidines (7)

7-alkylated-4-amino-5-cyanopyrrolo[2,3-*d*]pyrimidines can be prepared from 7-alkylated-4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidines **(6)** via catalytic hydrogenation. This procedure is illustrated in Scheme 3 and can be described in detail as follows.



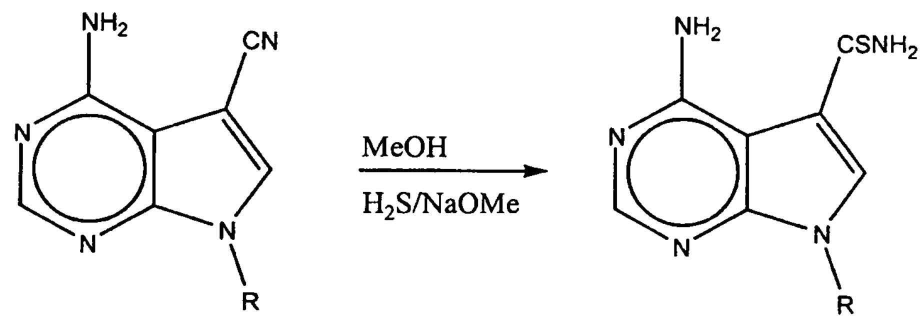
6 **7**

Scheme 3

To a mixture of EtOAc/EtOH (2:1 v:v) is added the 6-bromo compound with 1.0% Pd/C (10% by weight) and 1N NaOH. The mixture hydrogenated at room temperature and after 30 min. the mixture is filtered, washed with hot EtOAc (2 times) and the filtrate evaporated to dryness. The resulting solid is suspended in H_2O/MeOH (3:1 v:v) and heated to boiling. To this solution is added decolorizing charcoal which was filtered over Celite and the filtrate cooked overnight at 4°C. The resulting solid can be collected by filtration and dried overnight to yield the desired compound **(7)**.

c. General procedure to prepare 7-alkylated-4-amino-5-thiocarboxamidopyrrolo[2,3-*d*]pyrimidines **(8)**

The 7-alkylated-4-amino-5-thiocarboxamidopyrrolo[2,3-*d*]pyrimidines can be prepared from the corresponding **7** compounds by reacting with methanolic sodium sulfide in a sealed vessel at 95°C. Thus, dry H_2S is passed through a solution of sodium methoxide in dry methanol for 0.5 h. The **7** compound is added in one portion, and the mixture is stirred in a sealed pressure tube at 95°C for 2 h. The resulting solution is allowed to cool to room temperature, then adjusted to pH 7 with 1N HCl. The solvent is evaporated to dryness and the resulting compound **(8)** is recrystallized from H_2O containing a small amount of EtOH. This procedure is illustrated in Scheme 4.



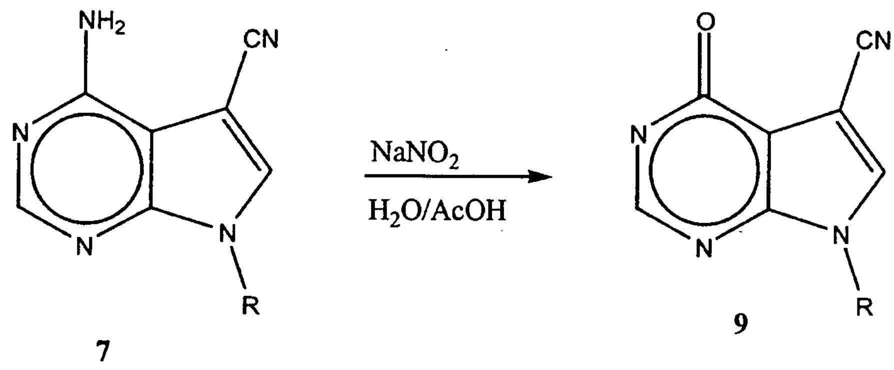
7 **8**

Scheme 4

Similarly, reaction of the **7** compound with methanolic sodium selenide would yield the selenoamide analogs.

d. General procedure to prepare 7-alkylated-4-oxo-5-cyanopyrrolo[2,3-*d*]pyrimidines **(9)**

A 7-alkylated-4-oxo-5-cyanopyrrolo[2,3-*d*]pyrimidines **(9)** can be prepared from a corresponding **7** compound, according to the general procedure shown in Scheme 5.



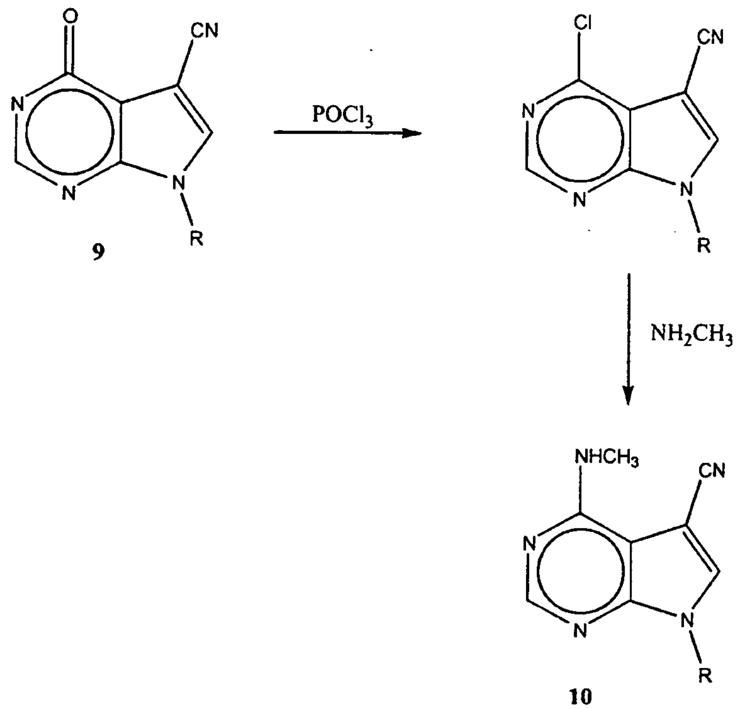
Scheme 5

The 7 compound is suspended in distilled H_2O and AcOH (about 11:1) and heated to 50°C and $NaNO_2$ is added batch-wise over a period of 4.5 h. Then, the reaction is heated to 70°C for 16 h. The resulting solid is cooled to 4°C for 24 h, collected by filtration and dried in vacuo at 60°C overnight to yield the desired 4-oxo product (**9**).

e. General procedure to prepare a 7-alkylated-4-methylamino-5-cyano pyrrolo [2,3-*d*]pyrimidine (**10**)

A 4-chloro compound is first prepared as follows. A corresponding **9** compound is dissolved in $POCl_3$ and the solution is heated at reflux for 12 min. The hot solution is poured onto ice water and the pH of the resulting mixture adjusted to 7 with NH_4OH (38%). The solution is extracted with CH_2Cl_2 (2 times) from distilled H_2O and $NaHCO_3$. The organic layer is collected and dried over $MgSO_4$, filtered and the filtrate evaporated to dryness. The solid is recrystallized from a MeOH/H_2O mixture and decolorizing charcoal to provide the 4-chloro compound.

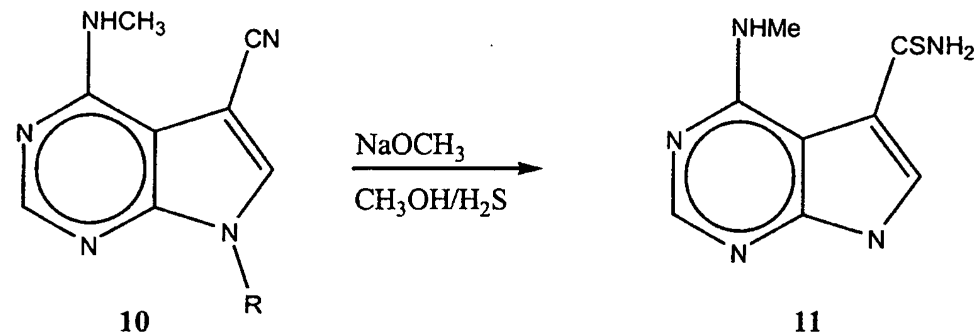
This 4-chloro compound is dissolved in methylamine (33% in abs. EtOH) and the solution stirred at room temperature for 2.5 h. The solution is then allowed to stand at 4°C for 16 h and the solid collected by filtration to furnish the product (**10**). This general procedure is illustrated in Scheme 6.



Scheme 6

f. General procedure to prepare 4-methylamino-7-alkylated-pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (11):

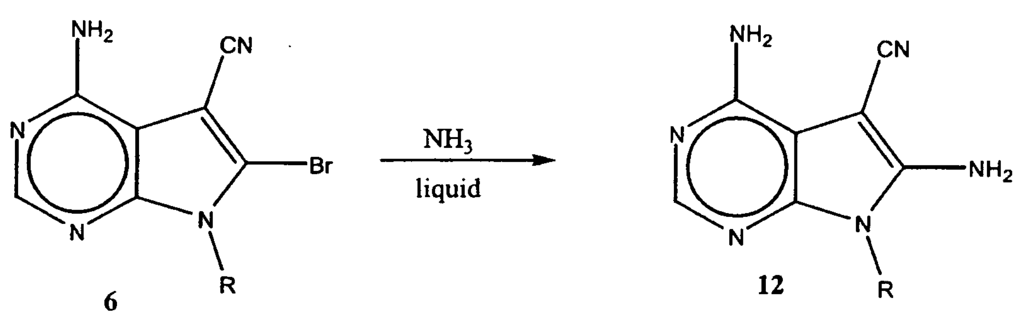
A 4-methylamino-7-(substituted)pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (**11**) can be prepared from its corresponding **10** compound as follows. NaOMe in dry MeOH is saturated with H_2S (g) for 30 min. This solution is transferred to a steel vessel containing a corresponding **10** compound. The vessel is sealed and heated at 100°C in an oil bath for 24 h. The solution is allowed to cool to room temperature and the pH adjusted to 7 with 1N HCl. To this solution is added silica which is applied to a column prepacked with silica. The column is eluted with hexanes/EtOAc (70:30, v:v) to afford **11**. The compound can be recrystallized from a H_2O/EtOH mixture to yield the product. This procedure is shown in Scheme 7.



Scheme 7

g. General procedure to prepare 4, 6-diamino-7-alkylated-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (12):

A corresponding **6** compound is placed in a steel vessel and the vessel is charged with liquid NH_3. The vessel should be sealed and the reaction heated at 100°C for 16 h. The vessel should be allowed to cool to room temperature and further cooled to -75°C at which time the vessel should be vented. The resulting solid is suspended in H_2O and heated to boiling. Following filtration, the filtrate is allowed to stand at 4°C for 16 h and the product **(12)** can be collected by filtration. This general procedure is illustrated in Scheme 8.

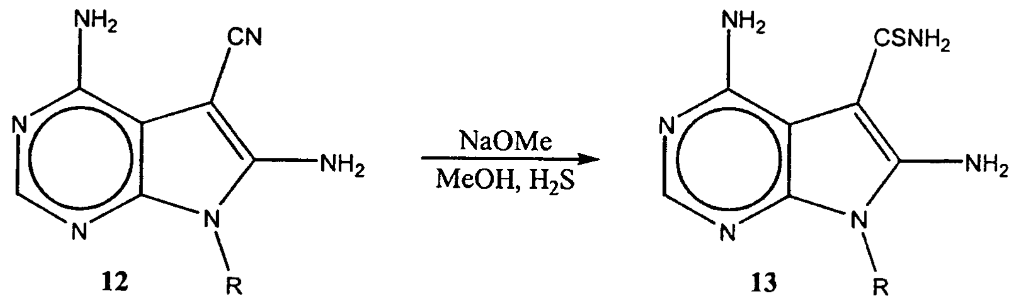


Scheme 8

h. General procedure to prepare 4,6-diamino-7-alkylated-pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (13):

NaOMe in dry MeOH is saturated with H_2S (g) for 30 min. This solution is transferred to a steel vessel containing the corresponding 4,6-diamino-7-alkylated-

pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile **(12)**. The vessel should be sealed and heated at 100°C in an oil bath for 19 h. The solution should be allowed to cool to room temperature and the pH of the solution adjusted to 7 with 1N HCl. The resulting solution should be evaporated to dryness and the solid recrystallized form H_2O/MeOH and decolorizing charcoal. This procedure is illustrated in Scheme 9.

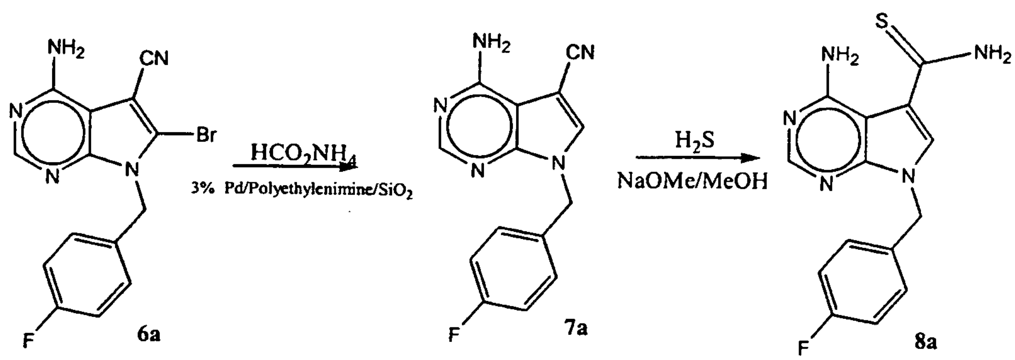


12 **13**

Scheme 9

The compounds disclosed and tested for antiviral activity (see, *infra*) have been prepared according to one or more of the above-described general procedures, or suitable modifications of the above-described general procedures. Such modifications are within the ordinary skill of the chemical and pharmaceutical arts.

An example of the application of the general procedures to prepare a specific compound is shown in Scheme 10, which illustrates the synthesis of 4-amino-5-thiocarboxamide-7-(4-fluorobenzyl)pyrrolo[2,3-*d*]pyrimidine.



6a **7a** **8a**

Scheme 10

Some additional specific examples are described below which further illustrate the invention.

2. Specific Examples of Chemical Synthesis

(i) 2-Amino-5-bromo-3,4-dicyanolpyrrole **(3)**

Compound **3** can be prepared according to Schemes 1 and 3, as discussed above. The more detailed procedure is as follows. A twelve-liter flask was fitted with an overhead stirrer, a condenser, a drying tube, and an internal thermometer. The flask was cooled in a MeOH/ice bath. Ethyl acetate (4 L), acetone (670 mL), and tetracyanoethylene **(1)** (128.09 g, 1 mol) were added. The solution was cooled to -10°C. HBr (1 L 33% w/w in AcOH, 4.1 M solution) was added dropwise at such a rate as to maintain the temperature at -10°C. A yellow solid began to precipitate during the addition. After the addition was complete, the suspension was stirred for an additional 3 hours. The yellow precipitate was collected by filtration, washed with ethyl acetate and ethyl ether, suspended in water (3 L), and was adjusted to pH 11 with 50% NaOH, giving a dark solution. Decolorizing charcoal was then added to the solution, filtered through Celite, and the filtrate was acidified to pH 5 with glacial acetic acid. The mixture was allowed to stand at 5°C for 18 hours. The product was then collected by filtration and oven dried (40°C, atmospheric pressure) for 7 days (117.4 g of brown solid, 56% yield): Mp: 180°C decomp. TLC: Rf=0.71 (2% MeOH/CH_2Cl_2), Rf=0.32 (EtOAc-Hexanes, 2:1).

(ii) 7-Alkyl-4-amino-6-bromo-5-cyanpyrrolo[2,3-*d*]pyrimidine **(6a-g)**

The preparation of compounds **6a-g** is illustrated in Scheme 1. Under an argon atmosphere, a mixture of 2-amino-5-bromo-3,4-dicyanopyrrole **(3)** (10.6 g, 50 mmol) and triethyl orthoformate (30 mL) in acetonitrile (300 mL) was heated under reflux for 3 hours at which time no starting material was detected by TLC. The solution was then concentrated under reduced pressure and coevaporated with toluene (3 X 125mL) to give a dark brown solid. The solid was then suspended in CH_2Cl_2 and filtered through a

bed Celite to remove particulate matter. The CH_2Cl_2 solution was then concentrated under reduced pressure to give a light brown solid, which was dissolved in dry THF (125 mL). Under an atmosphere of argon, the THF solution of 2-bromo-3,4-dicyano-5-(ethoxymethylene)iminopyrrole **(4)** (theoretical, 14.2 g, 50 mmol) was added dropwise to a stirred suspension of NaH (1.44 g, 60 mmol, 2.4 g of a 60% dispersion in mineral oil) in THF (30 mL).

On completion of addition, the solution was stirred for 20 minutes. Tetrabutylammonium iodide (3.0 g) was added, and then a solution of alkyl halide (60-75 mmol) was added. The mixture was heated under reflux for a minimum of 24 h and until no starting material was detected by TLC. The mixture was filtered through a bed of Celite to remove insolubles and concentrated under reduced pressure to a brown oil. This oil was dissolved in MeOH (100 mL) and 5N NH_3/MeOH (150 mL). The flask was sealed and the mixture stirred for a minimum of 48 h and until no uncyclized intermediate was detected by TLC. The product was isolated by filtration and recrystallized from AcOH. MP: 222-223°C.; UV/.lambda.max nm (/epsilon.mM): (pH 1) 282 (19.1); MeOH) 284 (22.1); (pH 11) 284 (19.1); 1 H NMR (DMSO-d6): a 9.23 (1H, s, H-2), 7.00 (2H, br s, NH_2), 5.58 (2H, s, NCH_2), 3.46-3.52 (2H, q, OCH2), 1.03-1.07 (3H, t, CH_2); Anal. Calc'd for $C_{10}H_{10}N_5BrO$: C, 40.56; H, 3.40; N, 23.65. Found: C, 40.70; H, 3.44; N, 23.58.

The following specific 7-alkylated-4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidines were prepared for compound **6** and its derivatives. All reactions where the intermediates were not isolated were assumed to be on the 50 mmol scale.

<u>(iii) 4-amino-6-bromo-5-cyano-7-(4-fluorobenzyl)pyrrolo[2,3-*d*]pyrimidine (**6a**, NE211)</u>

From 4-fluorobenzyl chloride (10.84 g, 75 mmol) was obtained **6a** after recrystallization from AcOH (3.06 g, 18% yield of off-white powder). Mp:263-265°C ref. Mp: 254-265°C. TLC: Rf=0.48 (EtOAc-Hexanes, 2:1) ^{1}H-NMR (300 MHz, dmso-d_6) δ 5.44 (s, 2H, CH_2), 7.04 (br.s, 3, NH_2), 7.14-7.20 (m, 2H, Ar), 7.24-7.27 (m, 2H, Ar), 8.23 (s, 1H, H-2).

(iv) 4-amino-6-bromo-5-cyano-7-(4-trifluoromethylbenzyl)pyrrolo[2,3-*d*]pyrimidine (**6b**, NE227)

From p-trifluoromethylbenzylchloride (10.0 g, 51 mmol) was obtained **6b** after recrystallization from AcOH (5.43 g, 34% yield of light pink powder). Mp: 274-275°C. TLC: Rf=0.556 (EtOAc-Hexanes, 2:1) ^{1}H-NMR (300 MHz, dmso-d_6) δ 5.60 (s, 2H, CH_2), 7.06 (s, 2H, NH_2), 7.36 and 7.72 (dd, 4H, Ar), 8.24 (s, 1H, H-2). Analysis calculated for $C_{15}H_9BrF_3N_5$: C, 45-46%; H, 2.29%; N, 17.67%. Found: C, 45.45%; H, 2.47%; N, 17.67%.

(v) 4-Amino-6-Bromo-5-cyano-7-(2-trifluoromethylbenzyl)pyrrolo[2,3-*d*]pyrimidine (**6c**, NE233)

From o-trifluoromethylbenzylchloride (10.0 g, 51 mmol) was obtained **6c** after recrystallization from AcOH (0.7 g, 5% yield of pink powder). Mp:280°C. Decomp. TLC: Rf=0.77 (EtOAc-Hexanes, 2:1) ^{1}H-NMR (300 MHz, dmso-d_6) δ 5.64 (s, 2H, CH_2), 6.47 (dd, 1H, Ar-4) 7.10 (br.s, 2H,NH_2), 7.54 (m, 2H, Ar-3+5), 7.84 (dd, 1H, Ar-2), 8.21 (s, 1H, H-2). Analysis Calculated for $C_{15}H_9BrF_7N_5$:. C, 45.46%; H, 2.29%; N, 17.67%. Found: C, 47.69%; H, 3.03%; N, 16.51%.

(vi) 4-amino-6-Bromo-5-cyano-7-(4-nitrophenethyl)pyrrolo[2,3-*d*]pyrimidine (**6d**, NE241)

From 4-nitrophenylethyl bromide (15.0 g, 65 mmol) was obtained **6d** after recrystallization from AcOH (0.7 g, 3.5% yield of white powder). Mp: 250-251°C. TLC: Rf=0.53 (EtOAc-Hexanes, 2:1) ^{1}H-NMR (300 MHz, dmso-d_6) δ 3.22 (t, 2H, CH_2), 4.51 (t, 2H, CH_2) 4.51 (t, 2H, CH_2), 6.96 (br.s., 2H, CH_2), 7.33-7.36 (d, 2H, Ar), 8.09-8.12 (d, 2H, Ar). 8,18 (s, 1H, H-2). Analysis Calculated for $C_{15}H_{11}BrF_6N_2$:. C, 46.51%; H, 2.87%; N, 21.70%. Found: C, 46.72%; H, 3.02%; N, 21.20%.

(vii) 4-Amino-6-Bromo-5-cyano-7-(4-chlorophenethyl)pyrrolo[2,3-*d*]pyrimidine (**6f**, NE253)

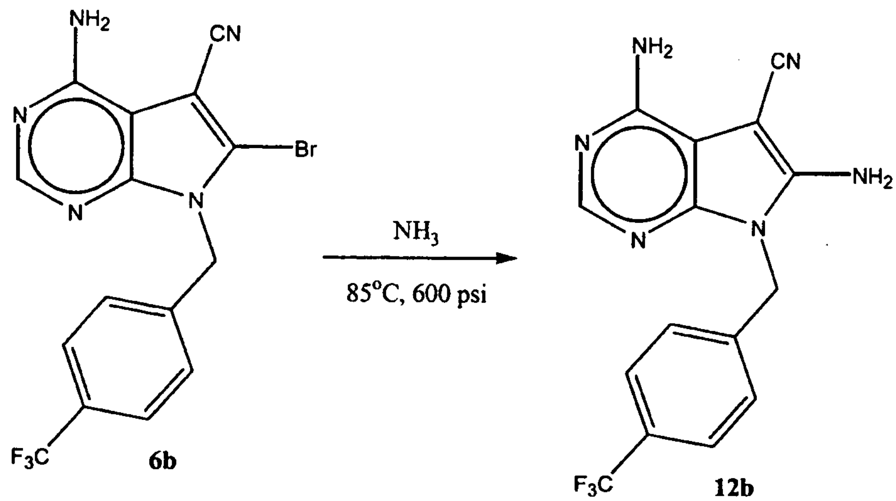
On a 25 mmol scale, 3,4-dicyano-5-(ethoxymethylene)iminopyrrole (7.1 g, 25 mmol) was prepared as described in the general procedure. This was then dissolved in CH_3CN (200 mL) and NaH (0.72 g, 30 mmol) was added slowly (in 20 mg portions) over a period of 15 minutes. 4-chlorophenylethyl chloride (7.00 g, 40 mmol) was then added and the solution stirred at 54°C for 10 days. The solution was then concentrated to a brown oil. This was then dissolved in 150 mL 5N NH_3 in EtOH, capped and stirred for 3 days. The product was recrystallized from AcOH (2.5 g, 26% yield of brown powder). Mp: 280°C decomp. TLC: Rf=0.54 (EtOAc-Hexanes, (2:1) ^{1}H-NMR (dmso-d_6) δ 3.06 (t, 2H, CH_2), 4.45 (t, 2H, CH_2) 6.95 (br, s, $2H_1$,CH_2), 4.45 (t, 2H, CH_2), 6.95 (br, s, $2H_1$, NH_2), 7.08 and 7.09 (d, 2H, Ar). 7.30 and 7.31 (d, 2H, Ar) 8.21 (s, 2H, H-2).

(viii) 4-Amino-6-bromo-5-cyano-7-(n-butyl)pyrrolo[2,3-*d*]pyrimidine (**6g**, NE270)

On a 25 mmol scale, 3,4-dicyano-5-(ethoxymethylene)iminopyrrole (7.1 g, 25 mmol) was prepared as described in the general procedure. This was then dissolved in CH_3CN (200 mL) and NaH (0.72 g, 30 mmol) was added slowly over a period of 15 minutes. N,N,N-trimethylbutylammonium iodide (6.87 g, 28 mmol) was then added and the solution stirred at reflux for 7 days. The solution was then concentrated, dissolved in 150 mL 5N ethanolic ammonia and left.

(ix) 5-cyano-4,6-diamino-7-(4-trifluoromethylbenzyl)pyrrolo[2,3-*d*]pyrimidine (**12b**, NE266)

Scheme 11 outlines the specific procedure to prepare **12b**.



Scheme 11

In a 500mL stainless steel vessel was placed **6b** (2.0 g, 5 mmol) and 250 mL of liquid ammonia. The vessel was sealed and heated at 85°C and 600 psi for 48 hours. The vessel was cooled to room temperature and vented. The solid obtained was collected and suspended in H_2O (75 mL). After stirring for 30 minutes the precipitate was collected by filtration and air-dried. The crude product was recrystallized from AcOH (0.39 g, 23% yield of white powder): Mp: 290°C sharp TLC: Rf=0.26 in EtOAc-Hexanes (2:1) ^{1}H-NMR (dmso-d_4) δ 5,39 (s, 2H, CH_2), 6.16 (s, 2H, 6-NH_2) 7.26 (s, 2H, 4-NH_2), 7.30 and 7.33 (d, 2H, Ar), 7.68 and 7.70 (d, 2H, Ar), 7.98 (s, 1H, H-2).

(x) Preparation of Alcohols (**16a-e**) from the Corresponding Carboxylic Acid (**15a-e**) by Reduction with Lithium Aluminum Hydride

The conversion of acids into alcohols is illustrated in Scheme 2, *supra*. The acids were dissolved in ethyl ether (100-500 mL) and added dropwise over a period of 1 hour to $LiAlH_4$ (1 equivalent) in ether (50 mL). The ethyl ether was kept below reflux with an ice bath as necessary. The reaction was stirred for a minimum of 2 hours and

until no starting material was detected by TLC. The reaction was quenched with water until the solution turned while and viscous. The suspension was then filtered through Celite and the ether filtrate was washed with water (500 mL), a 0.5 M HCl solution (500 mL), and dried over $MgSO_4$. The ether layer was concentrated under reduced pressure to yield the crude product which was then purified by vacuum distillation.

(xi) 4-Phenylbutyl alcohol (**16a**, NE230)

4-phenylbutyric acid (23.0 g, 0.14 mol) was used in the general procedure above. After distillation **16a** was obtained (17.66 g, 84% yield of clear colorless oil). Bp: 166°C (atmospheric pressure) TLC: Rf=0.44 (CH_2, Cl_2), ^{1}H-NMR (500 MHz, dmso-d_4) δ 1.4-1.7 (m, 4H, CH_2CH_2), 2.55 (t, 2H, ArCH_2) 3.36 (t, 2H, CH_2OH), 4.38 (s, 1H, OH), 7.13-7.25 (m, 5H, Ar).

(xii) 2-Chlorophenylethyl alcohol (**16b**, NE231)

2-Chlorophenylacetic acid (50.0 g, 0.29 mol) was used in the general procedure above. After distillation **16b** was obtained (39.53 g, 87% yield of clear colorless oil). Bp: 160°C (atmospheric pressure) TLC: Rf=0.50 (CH_2, Cl_2), ^{1}H-NMR (500 MHz, dmso-d_6) δ 2.86 (t, 2H, CH_2OH), 3.61 (t, 2H, ArCH_2) 4.78 (t, 1H, OH), 7.20-7.35 (m, 4H, Ar).

(xiii) 4-Chlorophenylethyl alcohol (**16c**, NE234)

4-Chlorophenylacetic acid (77.57 g, 0.455 mol) was used in the general procedure above. After distillation **16c** was obtained (67.54 g, 95% yield of clear colorless oil). Bp: 167°C (atmospheric pressure) TLC: Rf=0.40 (CH_2, Cl_2), ^{1}H-NMR (500 MHz, dmso-d_6) δ 2.72(t, 2H, CH_2OH), 3.60 (t, 2H, ArCH_2) 4.68 (telH, OH), 7.21-7.30 (m, 4H, Ar).

(xiv) 2,4-Dichlorophenylethyl alcohol (**16d**, NE236)

2,4-Dichlorophenylacetic acid (50.0 g, 0.244 mol) was used in the general procedure above. After distillation **16d** was obtained (39.72 g, 85% yield of clear

colorless oil). Bp: 186°C (atmospheric pressure) TLC: Rf=0.38 (CH_2, Cl_2), ^{1}H-NMR (500 MHz, dmso-d_6) δ 2.83 (t, 2H, CH_2OH), 3.60 (m, 2H, $ArCH_2$) 4.78 (t, 1H, OH), 7.30-7.35 (m, 2H, H-5+6), 7.50 (s, 1H, H-3).

(xv) 2-Fluorophenylethyl alcohol (**16e**, NE238)

2-Fluorophenylacetic acid (28.0 g, 0.182 mol) was used in the general procedure above. After distillation **16e** was obtained (22.94 g, 90% yield of clear colorless oil). Bp: 137°C (atmospheric pressure) TLC: Rf=0.38 (CH_2,Cl_2), ^{1}H-NMR (500 MHz, dmso-d_6) δ 2.78(t, 2H, CH_2OH), 3.63 (m, 2H, $ArCH_2$) 4.78 (t, 1H, OH), 7.10-7.30 (m, 4H Ar).

(xvi) Conversion of Alkyl Alcohols (**16a-e**) to Alkyl Chlorides (**17a-e**)

The purified alcohol was then dissolved in THF (100-500 mL) and added in one portion to $SOCl_2$ (1:20 equivalents) in THF (50 mL). LiCl (1 g) was added and the solution was heated at reflux for 2 hours. The reaction was then dissolved in water (500 mL) and ethyl ether (500 mL) and the ether layer was washed with saturated solution of $NaHCO_3$ (Sat. Soln.), 0.5 M HCl solution (pH 2) and dried over $MgSO_4$. The ether layer was concentrated under reduced pressure to a light yellow oil. The crude product was purified by vacuum distillation.

(xvii) 1-Chloro-4-phenylbutyl chloride (**17a**, NE242)

4-phenylbutyl alcohol (17.66 g, 0.12 mol) was used in the general procedure above. After distillation **17a** was obtained (12.15 g, 60% yield of clear colorless oil). Bp: 152°C (atmospheric pressure) TLC: Rf=0.86 (CH_2Cl_2), ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.91 (t, 4H,$CH1_2CH_2$), 2.76(T,2H, CH_2Cl) 3.65 (t, 2H, arCH_2), 7.30-7.55 (m, 5H Ar).

(xviii) 2-Chlorophenylethyl chloride (**17b**, NE244)

2-Chlorophenylethyl alcohol (39.53 g, 0.252 mol) was used in the above general procedure. After distillation **17b** was obtained (39.09 g, 89% yield of clear slightly

yellow oil): Bp: 160°C (atmospheric pressure) TLC: Rf=0.86 (CH_2Cl_2). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.11 (t, 2H, CH_2Cl), 3.67 (t. 2H, $ArCH_2$), 7.10-7.20 (m, 4H, Ar).

(xix) 4-Chlorophenylethyl chloride (**17c**, NE246)

4-Chlorophenylethyl alcohol (67.54 g, 0.43 mol) was used in the above general procedure. After distillation **17c** was obtained (60.88 g, 81% yield of clear colorless oil): Bp: 147°C (atmospheric pressure) TLC: Rf=0.89 (CH_2Cl_2). ^{1}H-NMR (500 MHz, dmso-d_6) δ 3.02(t, 2H, CH_2Cl), 3.83(t, 2H, $ArCH_2$), 7.27-7.36 (m, 4H, Ar).

The following additional compounds were prepared according to the above described general methods.

4-Amino-6-bromo-7-(ethoxymethyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (JJ 164); 4-Amino-6-bromo-7-[(2-methyoxyethoxy)methyl]pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (JJ 194); 4-Amino-6-7-(benzyloxymethyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (JJ 078); 4-Amino-6-bromo-7-(benzyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile(LI 90); 4-Amino-6-bromo-7-(4-methylbenzyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (LI 126); 4-Amino-6-bromo-7-(3-methylbenzyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (JJ 022); 4-Amino-6-bromo-7-(2-methylbenzyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (MC 158); 4-Amino-6-bromo-7-(4-tert-butylbenzyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (MC 160); 4-Amino-6-bromo-7-(4-methoxybenzyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (MC 166); 4-Amino-7-(ethoxymethyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (JJ 176); 4-Amino-7-[(2-methoxyethoxy)methyl]pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (JJ 202); 4-Amino-7-(benzyloxymethyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (LI 240); 4-Amino-7-(benzyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (LI 110); 4-Amino-7-(4-methylbenzyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (LI 130); 4-Amino-7-(3-methylbenzyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (MC 168); 4-Amino-7-(2-methylbenzyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (LI 246); 4-Amino-7-(4-tert-butylbenzyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (JJ 104); 4-Amino-7-(4-methoxybenzyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (JJ 092); 4-Amino-7-

(ethoxymethyl)pyrrolo[2,3-*d*]pyrimidine-5-carboxamide (LI 216); 4-Amino-7-[(2-methoxyethoxy)methyl]pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (JJ 048); 4-Amino-7-(benzyloxymethyl)pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (LI 250); 4-Amino-7-(benzyl)pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (LI 128); 4-Amino-7-(4-methylbenzyl) pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (LI 144); 4-Amino-7-(3-methylbenzyl)pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (JJ 072); 4-Amino-7-(2-methylbenzyl)pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (JJ 026); 4-Amino-7-(4-tert-butylbenzyl)pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (JJ 114); 4-Amino-7-(4-methylbenzyl)pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (JJ 098); 4-Amino-7-(ethoxymethyl)pyrrolo[2,3-*d*]pyrimidine-5-selenocarboxamide; 5-Cyano-7-(ethoxymethyl)pyrrolo[2,3-*d*]pyrimidine-4-one (JJ 178); 5-Cyano-7-[(2-methoxyethoxy)methyl]pyrrolo[2,3-*d*]pyrimidine-4-one (JJ 192); 4-Chloro-7-(ethoxymethyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (JJ 172); 4-Chloro-7-[(2-methoxyethoxy)methyl]pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (JJ 242); 4-Methylamino-7-(ethoxymethyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (JJ 278); 4-Methylamino-7-[(2-methoxyethoxy)methyl]pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (MC 014); 4-Methylamino-7-(ethoxymethyl)pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (MC 032); 4-Methylamino-7-[(2-methoxyethoxy)methyl] pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (MC 030); 4,6-Diamino-7-(ethoxymethyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (JJ 028); 4,6-Diamino-7-[(2-methoxyethoxy)methyl]pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (JJ 070); 4,6-Diamino-7-(benzyloxymethyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (JJ 082); 4,6-Diamino-7-(ethoxymethyl)pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (JJ 076); 4,6-Diamino-7-[(2-methoxyethoxy)methyl]pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (JJ 088); and 4,6-Diamino-7-(benzyloxymethyl)pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (JJ 100).

The above reaction schemes and procedures are for illustrative purposes only and should not be considered as limiting in any way the scope of the invention disclosed herein. Moreover, the pyrrolo[2,3-*d*]pyridines disclosed herein can be prepared by other methods than those disclosed hereinabove, wherein such other methods are known to

those of ordinary skill in the art. For further guidance, see Swayze, E.E. *et al.*, *in:* Nucleic Acid Chemistry; Improved And New Synthetic Procedures, Methods And Techniques, L.B. Townsend and R.S. Tipson (Eds), Part IV, pp. 16-18, Wiley-Interscience, New York, (1991), and U.S. Patent No. 5,543,413, the contents of which are incorporated by reference herein to further illustrate the synthetic aspects of the present invention.

D. *In Vitro* Antiviral Evaluation Methods.

(a) Cells and Viruses

The routine growth and passage of KB and BSC-1 cells was performed in monolayer cultures using minimal essential medium (MEM) with either Hanks salts [MEM(H)]or Earle salts [MEM(E)] supplemented with 10% calf serum. The sodium bicarbonate concentration was varied to meet the buffering capacity required. Cultures of diploid human foreskin fibroblast (HFF) or MRC-5 cells were grown in medium consisting of MEM(E) with 10% fetal bovine serum. Cells were passaged at 1:2 to 1:10 dilutions according to conventional procedures by using 0.05% trypsin plus 0.02% EDTA in a HEPES buffered salt solution (HBS) (see, Shipman, C., Jr., *Proc. Soc. Exp. Biol.* 130:305-310 (1969)) as described previously (Turk, S.R. *et al.*, *Antimicrob. Agents Chemother.* 31:544-550 (1987)). HFF and MRC-5 cells were passaged only at 1:2 dilutions. The Towne strain, plaque-purified isolate Po, of HCMV was kindly provided by Dr. Mark Stinski, University of Iowa. The KOS strain of HSV-1 was used in most experiments and was provided by Dr. Sandra K. Weller, University of Conn.

(b) Virological procedures

Stock HCMV was prepared by infecting HFF cells at a multiplicity of infection (m.o.i.) of <0.01 plaque-forming units (p.f.u.) per cell. Cell growth medium was changed every four days until cytopathology was evident in all cells (approximately 21 days). Supernatant fluids were retained as the virus stock.

High titer HSV-1 stocks were prepared by infecting BSC cells at an m.o.i. of <0.1 as detailed previously. See, Turk, S.R. *et al.*, *Antimicrob. Agents Chemother.* 31:544-550 (1987).

Virus titers were determined using monolayer cultures of HFF cells for HCMV and monolayer cultures of BSC-1 cells for HSV-1 as described earlier (Prichard, M.N. *et al.*, *J. Virol. Meth.* 28:101-106 (1990)). Briefly, HFF or BSC-1 cells were planted as described as above in 96-well cluster dishes and incubated overnight at 37°C in a humidified 3% CO_2-97% air atmosphere. The next day cultures were inoculated with HCMV or HSV-1 and serially diluted 1:3 across the remaining eleven columns of the 96-well plate. Cultures were incubated at 37°C for 2 h to permit virus adsorption and then virus inoculum was replaced with 0.2 ml of fresh medium. Cultures were incubated for seven days for HCMV, two or three days for HSV-1. The medium was removed, and the cell sheets were stained with 0.1% crystal violet in 20% methanol.

HCMV plaques were enumerated under 20-fold magnification in wells having the dilution that gave 5 to 20 plaques per well. HSV-1 plaques were counted with the unaided eye or at 3-10 fold magnification. Virus titers were calculated according to the following formula: Titer (p.f.u./ml) = number of plaques x 5 x 3n; where n represents the *nth* dilution of the virus used to infect the well in which plaques were enumerated.

(c) Assays for antiviral activity

1. HCMV plaque reduction assay

HFF cells in 24-well cluster dishes were infected with approximately 100 p.f.u. of HCMV per cm^2 cell sheet using the procedures detailed above. Following virus adsorption, compounds dissolved in growth medium were added to duplicate wells in four to eight selected concentrations. After incubation at 37°C for 7 to 10 days, cell sheets were fixed, stained with crystal violet and microscopic plaques enumerated as described above. Drug effects were calculated as a percentage of reduction in number of plaques in the presence of each drug concentration compared in the number observed in the absence of drug.

2. HCMV yield assay

HFF cells were planted as described above in 96-well cluster dishes, incubated overnight, medium removed and the cultures were inoculated with HCMV at an m.o.i. of 0.5 to 1 p.f.u. per cell as reported elsewhere (see, Prichard, M.N. *et al.*, *J. Virol. Meth.* (1990) *28*:101-106). After virus adsorption, inoculum was replaced with 0.2 mL of fresh medium containing test compounds. The first row of 12 wells was left undisturbed and served as virus controls. Each well in the second row received an additional 0.1 mL of medium with test compound at three times the desired final concentration. The contents of the 12 wells were mixed by repeated pipetting and then serially diluted 1:3 along the remaining wells. In this manner, six compounds could be tested in duplicate on a single plate with concentrations from 100 mM to 0.14 mM. Plates were incubated at 37°C for seven days, subjected to one cycle of freezing and thawing; aliquots from each of the eight wells of a given column were transferred to the first column of a fresh 96-well monolayer culture of HFF cells. Contents were mixed and serially diluted 1:3 across the remaining eleven columns of the secondary plate. Each column of the original primary plate was diluted across a separate plate in this manner. Cultures were incubated, plaques were enumerated, and titers calculated as described above.

3. HSV-1 ELISA

An ELISA was employed (see, Prichard, M.N. and Shipman, C., Jr., *Antiviral Res.* (1990) *14*:181-206) to detect HSV-1. Ninety-six (96)-well cluster dishes were planted with 10,000 BSC-1 cells per well in 200 μL per well of MEM(E) plus 10% calf serum. After overnight incubation at 37°C, selected drug concentrations in quadruplicate and HSV-1 at a concentration of 100 p.f.u./well were added. Following a three (3) day incubation at 37°C, medium was removed, plates were blocked, rinsed, and horseradish peroxidase conjugated rabbit anti-HSV-1 antibody was added. Following removal of the antibody containing solution, plates were rinsed, and then developed by adding 150 μL per well of a solution of tetramethylbenzidine as substrate. The reaction was stopped with H_2SO_4 and absorbance was read at 450 and 570 nm.

Drug effects were calculated as a percentage of the reduction in absorbance in the presence of each drug concentration compared to absorbance obtained with virus in the absence of drug.

4. HHV-6 ELISA

An enzyme-linked immunosorbent assay (ELISA) is performed in covalent amine plates (Costar, Cambridge, MA). The plates are activated by the addition of a homobifunctional cross-linking agent, bis(sulfosuccinimidyl) suberate and then washed with PBS. Samples consisting of 150 µL of suspended HSB2 cells are infected with HHV-6 and previously incubated with drug on a separate plate are solubilized in Triton X-100 in coating buffer. The plate is covered and incubated for 1 h at 37°C in a 5% CO_2 atmosphere. These binding conditions facilitate covalent attachment of the antigen to the free end of the crosslinker. After covalent binding, the antigen solution is decanted and the plate is washed six times in HEPES buffered saline (see, Shipman, C., Jr., *Proc. Soc. Exp. Biol.* (1969) *130*:305-310) with 0.05% Tween 20 (HBS-T), and soaked for three minutes for each wash. Unbound sites on the plate are blocked, the blocker decanted, and diluted primary monoclonal antibody, specific for HHV-6 **(GS)** is added. The plate is then covered and incubated for 1 h at 37°C. The plate is washed again, blocker is added again, and horseradish peroxidase-labeled rabbit anti-mouse antibody added to each well. The plate is incubated for 1 h at 37°C, washed again as described above, and developed using TMB-Turbo (Pierce, Rockford, IL) for 30 min at room temperature. The reaction is stopped with 2M H_2SO_4. Absorbance in each well is determined at 450/570 nanometers.

5. HIV-1

The assay measures the presence of HIV in supernatants of CEM cells (ATCC) infected with strain IIIB of HIV-1 by the amount of RT activity. Reverse transcriptase (RT) is employed as a marker for HIV-1. Cells are grown, infected, and incubated in the presence of seven concentrations (one-half log 10 dilutions) beginning at 1 or 100 µM of compounds to be assayed. Procedures and the RT assay are performed as

detailed in Kucera, L.S. *et al.*, *AIDS Res. Human Retroviruses* (1993) *9*:307-314; and White, E.L., *et al.*, *Antiviral Res.* (1991) *16*:257-266.

Although the compounds are shown to be particularly effective against HCMV and HSV-1, it is within the scope of this invention that other viruses are effectively treated with the compounds of this invention by use of methods described herein and others well known to those of skill in the art. Other viruses that can be treated as defined herein and within the scope of the present invention include all members of the herpes family, and human immunodeficiency virus (HIV) and hepatitis viruses, for example, hepatitis B virus (HBV). Methods of determining the efficacy of any of the compounds of this invention against HBV are well known in the art. See for example, the methods shown in U.S. Patent No. 5,399,580 to Daluge.

An additional member of the hepatitis family that can be treated as defined herein is hepatitis C virus (HCV). U.S. Patent No. 5,679,342, issued to Houghton *et al.* describes in detail, methods of employing an extracorporeal cell system infected with HCV to screen for the compounds most active against HCV. In brief, the method comprises: (a) providing a composition containing the compound of this invention to be tested; (b) providing an extracorporeal cell system capable of being infected by HCV; (c) providing a biological sample containing infective HCV; (d) incubating the compositions of (a) and (c) with the cell system of (b) under conditions that would, in the absence of (a), allow infection of HCV in the cell system; and (e) detecting inhibition of viral infection after incubation. Preferred cell systems, as disclosed in U.S. Patent No. 5,679,342, include hepatocytes, macrophages, more preferably Kupffer macrophages, and B lymphocytes. Cell lines derived from organs of hepatocytic origin also are suitable for use in the assay described above. One can also use the above noted assay to test for the inhibition of viral replication by incubating the compositions of (a) and (b) under conditions that would, in the absence of (a), allow replication of HCV in the cell line and then detecting inhibition of viral replication after incubation.

Another method, well known in the art, for testing the antiviral activity of compounds against HCV is the helicase inhibition assay described, for example, in Lain

et al. (1991) *Nucleic Acids Res.* 69:1720-1726 and Kim *et al.* (1955) *Biochem. Biophys. Res. Comm.* 160-166.

When the method is practiced *in vivo* in a subject, such as a human patient, the compound can be added to a pharmaceutically acceptable carrier and systemically or topically administered to the subject, such as a human patient or a mammal such as a mouse, a rat, a woodchuck, or a simian.

The compositions also can be administered to subjects or individuals susceptible to, or at risk for, viral infection, such as HCMV, HSV-1 or herpes virus infection. Thus, this invention also provides a prophylactic method of inhibiting viral replication, proliferation and/or viral infection in a subject by administering to a subject a prophylactic effective amount of the compound or composition under suitable conditions such that viral replication, proliferation or infection is inhibited. A "prophylactically effective amount" is an amount that inhibits viral infection, reproduction and proliferation in a subject challenged with the virus, without toxicity to the cells and subject being treated.

(d) Cytotoxicity assays.

Two different assays were used to explore cytotoxicity of selected compounds: (i) Cytotoxicity produced in stationary HFF cells was determined by microscopic inspection of cells used in plaque assays which were not affected by the virus (Turk, S.R., *et al.*, *Antimicrob. Agents Chemother.* 31:544-550, 1987), and (ii) The effect of compounds during two population doublings of KB cells was determined by crystal violet staining and spectrophotometric quantitation of dye eluted from stained cells as described in, for example, Prichard, M.N., *et al.*, *Antimicrob. Agents Chemother.*, 35:1060-1065 (1991).

Briefly, 96-well cluster dishes were planted with KB cells at 3000-5000 cells per well. After overnight incubation at 37°C, test compound was added in quadruplicate at six to eight concentrations. Plates were incubated at 37°C for 48 hours in a CO_2 incubator, rinsed, fixed with 95% ethanol, and stained with 0.1% crystal violet.

Acidified ethanol was added and plates read at 570 nm in a spectrophotometer designed to read 96-well ELISA assay plates.

(e) Data analysis

Dose-response relationships were constructed by linearly regressing the percent inhibition of parameters derived in the preceding sections against logarithm 10 drug concentrations. Fifty percent inhibitory (IC50) concentrations were calculated from the regression lines (see, Goldstein, A., *Biostatistics: An Introductory Text*, MacMillan, New York, pp. 156-161 (1964)). Samples containing positive controls (acyclovir for HSV-1 and ganciclovir for HCMV) were used in all assays.

2. Results

(a) Antiviral evaluation

Compounds were evaluated for activity against human cytomegalovirus (HCMV) and herpes simplex virus type 1 (HSV-1). The cytotoxicity of each compound was determined as detailed above in both human foreskin fibroblasts (HFF cells) and in KB cells. These results are presented in Table 1.

Table 1

Compound No.*	HCMV	HSV-1	HFF	KBgrv
1414	17	45	>120	20
1429	1.8	33	>100	60
1444	0.8	85	>10	>100
1360	1.6	>100	>10	>100
1382	>10	>100	>10	>100
659	171.33	32.6	118	75
1428	38	50	45	20
636	14.50	>100	100	222
826	222.00	>100	222	222
658	181.33	>100	141	222

Compound No.*	HCMV	HSV-1	HFF	KBgrv
845	28	50	100	1
839	13.00	35	127	47
1419	4.2	16	100	50
1412	5	45	100	>100
1421	42	>100	>100	>100
1441	21	90	100	16
1363	2.7	90	>100	50
1353	1.4	60	116.5	>100
1443	>10	>100	>10	>100
1388	116.5	>100	116.5	>100
1461	>100	>100	>100	>100
1462	>100	>100	>100	>100
1373	10.5	>100	10.5	>100
1331	>10	>100	>10	>100
1374	>10	>100	>10	>100
1427	>10	>100	>10	>100
1451	12	50	>100	40
1365	.3	33	>100	60
1356	.2	17.041	46	76
1389	.2	>100	>10	15
1348	.6	155.92	>10	>100
1352	>100	100	>100	146
1425	5	>100	>100	>100
1455	6.5	>100	>100	40
1368	.7	10	32	>100
1396	17	45	>100	40
1446	<1	0.65	100	10

Compound No.*	HCMV	HSV-1	HFF	KBgrv
1463	>10		>10	
1351	1	222	>100	>100
1409	100	>100	>100	>100
1369	<0.1	0.3	100	82
1413	.5	1.5	32	38
1376	28	35	100	70
1362	>10	>100	>10	>100
1347	>10	222	>10	>100
1350	5	121	>100	50
1372	>10	>100	>10	>100
1361	>100	>100	>100	>100
1329	19	40	46	33

*The compound no. in column 1, refers to the structure as described in the detailed description above. For example, compound 1414 represents 4-amino-7-(1-methylbenzyl)-5-carbonitrile.

In general, the 4-substituted-benzyl group at the N7 position produced good to excellent antiviral activity against HCMV. See compounds 1429, 1444, 1360, 1536, 1428, 839, 1419, 1412, 1363, 1352, 1365, 1356, 1389, and 1348. Of these compounds, many of those with an electron withdrawing group, such as a halo, or nitro group at the 4-position of the benzyl group show excellent activity. See, for example, compounds 1429, 1444, 1360, 1352, 1356, 1365, 1389, and 1348. This is a novel finding of this invention.

In addition, the data reveal that, surprisingly, those compounds with a N7 substitution having an aralky group with longer alkyl chain such as phenethyl, or phenpropyl also showed excellent activity against HCMV. See, for example, compounds 1368, 1446, 1351, 1369, 1413, and 1350.

The antiviral activity is also influenced by the substitutions at other positions on the pyrrolo[2,3-*d*]pyrimidine ring. For example, the longer alkyl chain phenyl at the 7-

position is lost if the cyano group at the 5-position of the pyrrolo[2,3-*d*]pyrimidine is replaced with another nitro group such as a carboxamido group. See, for example, compound 1409.

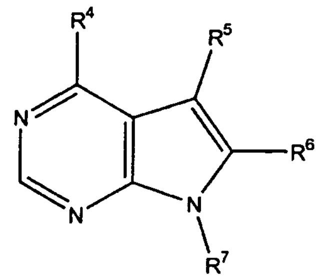
Some activity was also seen in compounds having a 3-substituted benzyl group. See compounds 1455 (having a 3-amino benzyl) and 1425 (having a 3-nitrobenzyl).

From the above data, which shows that compounds with an electron withdrawing group at the 4-position of a benzyl and compounds with a longer alkyl chain to attach a phenyl group to the N7 position of the pyrrolo[2,3-*d*]pyrimidine have excellent antiviral activity. Compounds having both the desirable features (*i.e.*, compounds possessing an aralkyl group at the N7-position wherein the alkyl chain has greater than 2 carbons and the phenyl ring is substituted with various one or more electron-withdrawing groups) would have enhanced antiviral activity are within the scope of this invention. Such compounds would include for example: 4-amino-7-(2-(4-fluorophenyl))ethyl-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-7-(3-4-fluorophenyl)-propyl)-pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide; 4-6-diamino-7-((2-(4-fluorophenyl))ethyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-6-bromo-7-((2-(4-fluorophenyl))ethyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 4-amino-7-((2-(4-fluorophenyl))ethyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; and 4-amino-7-(3-(4-fluorophenyl)-propyl)-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide, among others. Since this invention provides methods for preparing such compounds and methods to evaluate their antiviral activity, such compounds are also within the scope of this invention.

CLAIMS

We claim:

1. A compound having the structure:



wherein:

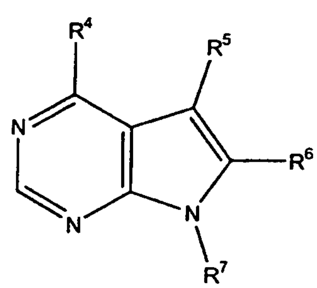
R^4 is $-NR_1R_2$ or oxo;

R^5 is -CN, $-CSNR_1R_2$ or $-CONR_1R_2$ but not $-CONH_2$;

R^6 is -H or halo, or $-NR_1R_2$;

wherein R_1 and R_2 are independently -H or an aliphatic group; and R^7 is of the formula R_3-Ar, wherein R_3 is an aliphatic group and Ar is an unsubstituted aryl or an aryl independently substituted with halo, nitro, amino, or aliphatic groups; and pharmaceutically acceptable salts, prodrugs and derivatives thereof.

2. A compound having the structure:



wherein

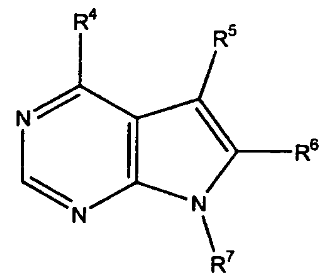
R^4 is $-NR_1R_2$ or oxo;

R^5 is -CN or $-CSNR_1R_2$;

R^6 is -H, or halo, or $-NR_1R_2$;

wherein R_1 and R_2 are independently -H or an aliphatic group; and R^7 is of the formula R_3-Ar, wherein R_3 is an aliphatic group and Ar is an unsubstituted aryl or an aryl independently substituted with halo, nitro, amino, or aliphatic groups; provided that when R^6 is an -H or $-NH_2$, and Ar is $-C_6H_5$ or a phenyl substituted with only one aliphatic group, R_3 is an aliphatic group other than methyl such that $-R_3-$ is not a $-CH_2-$; and pharmaceutically acceptable salts, prodrugs and derivatives thereof.

3. A compound having the structure:



wherein:

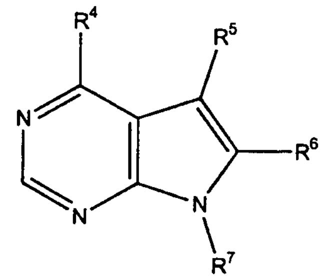
R^4 is $-NR_1R_2$ or oxo;

R^5 is -CN, $-CSNR_1R_2$ or $-CONR_1R_2$ but not $-CONH_2$;

R^6 is halo;

wherein R_1 and R_2 are independently -H or an aliphatic group; and R^7 is of the formula R_3-Ar, wherein R_3 is an aliphatic group and Ar is an unsubstituted aryl or an aryl independently substituted with halo, nitro, amino, or aliphatic groups; provided that when R^6 is bromo and Ar is a $-C_6H_5$ or a phenyl substituted with only one aliphatic group, R_3 is an aliphatic group other than methyl; and pharmaceutically acceptable salts, prodrugs and derivatives thereof.

4. A compound having the structure:



wherein:

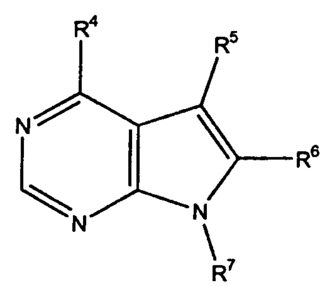
R^4 is $-NR_1R_2$ or oxo;

R^5 is -CN, $-CSNR_1R_2$ or $-CONR_1R_2$;

R^6 is -H or halo, or $-NR_1R_2$;

wherein R_1 and R_2 are independently -H or an aliphatic group; and R^7 is of the formula R_3-Ar, wherein R_3 is an aliphatic group and Ar is an aryl independently substituted with halo, nitro, amino groups; and pharmaceutically acceptable salts, prodrugs and derivatives thereof.

5. A compound having the structure:



wherein:

R^4 is $-NR_1R_2$ or oxo;

R^5 is -CN, $-CSNR_1R_2$ or $-CONR_1R_2$;

R^6 is -H or halo, or $-NR_1R_2$;

wherein R_1 and R_2 are independently -H or an aliphatic group; and R^7 is of the formula R_3-Ar, wherein R_3 is an aliphatic group and Ar is an unsubstituted aryl or an aryl independently substituted with halo, nitro, amino, or aliphatic groups; provided that R_3 is an aliphatic group other than methyl such that $-R_3-$ is not a $-CH_2-$; and pharmaceutically acceptable salts, prodrugs and derivatives thereof.

6. The compound of claim 2, wherein:

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH(CH_3)-C_6H_4$ (1414);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-C_6H_4$-4-F (1429);

R^4 is NH_2; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-C_6H_4$-4-Cl (1444);

R^4 is NH_2; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-C_6H_4-4-NO_2$ (1360);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is$-CH_2-C_6H_4-3-NO_2$ (1362);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-(CH_2)_3-C_6H_5$ (1350);

R^4 is $-NH_2$; R^5 is $-CSNH_2$; R^6 is -H; and R^7 is $-CH_2-CH_2-C_6H_5$ (1446);

R^4 is $-NH_2$; R^5 is $-CSNH_2$; R^6 is -H; and R^7 is $-CH_2-CH_2-CH_2-C_6H_5$ (1413);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-CH_2-C_6H_5$ (1368);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH(CH_3)-C_6H_5$ (1451);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-CH_2-C_6H_5$ (1369);

R^4 is $-NHCH_3$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2\,C_6-H_4-3-NO_2$ (1425);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4-3-NH_2$ (1455);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$ and R^7 is $-CH_2-C_6H_4$-4-F (1365);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4$-4-Cl (1356);

R^4 is NH_2; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4$-4-Br (1389);

R^4 is NH_2; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2C_6H_4-4-NO_2$ (1348);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4-4-NH_2$ (1352);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-CH=CH-CH_2-C_6H_5$ (1372);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-CH=CH-CH_2-C_6H_5$ (1329);

R^4 is -oxo; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-CH_3$ (1441);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH(CH_3)-C_6H_5$ (1363);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-F$ (1353);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-Cl$ (1355);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2C_6H_4-3-Cl$ (1461);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_3-3,4-(Cl)_2$ (1462);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-Br$ (1373);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-NO_2$ (1374);
R^4 is $-NH-CH_3$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-CH_2-C_6H_5$ (1463);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-CH_2-C_6H_5$ (1351);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-(CH_2)_3-C_6H_5$ (1347); and
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-CH=CH-C_6H_5$ (1361).

7. The compound of claim 3 wherein:

R^4 is -oxo; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-CH_3$ (1441);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH(CH_3)-C_6H_5$ (1363);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-F$ (1353);
R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-Cl$ (1443);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-Cl$ (1355);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2C_6H_4-3-Cl$ (1461);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_3-3,4-(Cl)_2$ (1462);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-Br$ (1373);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-NO_2$ (1374);
R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-CH_3$ (1427);
R^4 is $-NH-CH_3$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-CH_2-C_6H_5$ (1463);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-CH_2-C_6H_5$ (1351);
R^4 is NH_2; R^5 is $-CONH_2$; R^6 is -Br; and R^7 is $-CH_2-CH_2-C_6H_5$ (1409);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-(CH_2)_3-C_6H_5$ (1347); and
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-CH=CH-C_6H_5$ (1361).

8. The compound of claim 4, wherein:

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-C_6H_4-4-F$ (1429);

R^4 is NH_2; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-C_6H_4-4-Cl$ (1444);

R^4 is NH_2; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-C_6H_4-4-NO_2$ (1360);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is$-CH_2-C_6H_4-3-NO_2$ (1362);

R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2C_6H_4-4-F$ (1419);

R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2-C_6H_4-4-NO_2$ (1412);

R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2-C_6H_4-3-NO_2$ (1421);

R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-Cl$ (1443);

R^4 is $-NH_2$; R^5 is-CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-Cl$ (1388);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2C_6H_4-3-Cl$ (1461);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_3-3,4-(Cl)_2$ (1462);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-Br$ (1373);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-NO_2$ (1331);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-C_6H_4-4-NO_2$ (1374);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$ and R^7 is $-CH_2-C_6H_4-4-F$ (1365);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4-4-Cl$ (1356);

R^4 is NH_2; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4-4-Br$ (1389);

R^4 is NH_2; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4-4-NO_2$ (1348);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4-4-NH_2$ (1352);

R^4 is $–NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4-3-NO_2$ (1425); and

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-C_6H_4-3-NH_2$ (1455).

9. The compound of claim 5, wherein:

R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH(CH_3)-C_6H_5$ (1363);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH(CH_3)-C_6H_5$ (1451);

R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-CH_2-C_6H_5$ (1368);

R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2-CH_2-C_6H_5$ (1396);

R^4 is $-NH_2$; R^5 is - $CSNH_2$; R^6 is -H; and R^7 is $-CH_2-CH_2-C_6H_5$ (1446);

R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-CH_2-C_6H_5$ (1369);

R^4 is $-NH_2$; R^5 is $-CSNH_2$; R^6 is -H; and R^7 is $-CH_2-CH_2-CH_2-C_6H_5$ (1413);
R^4 is $-NH_2$; R^5 is $-CONH_2$; R^6 is -H; and R^7 is $-CH_2-CH_2-CH_2-C_6H_5$ (1376);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-C_6H_5-CH_2-CH_2$ (1362);
R^4 is $-NH-CH_3$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-CH_2-C_6H_5$ (1463);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-CH_2-C_6H_5$ (1351);
R^4 is NH_2; R^5 is $-CONH_2$; R^6 is -Br; and R^7 is $-CH_2-CH_2-C_6H_5$ (1409);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-(CH_2)_3-C_6H_5$ (1347);
R^4 is $-NH_2$; R^5 is -CN; R^6 is -Br; and R^7 is $-CH_2-CH=CH-C_6H_5$ (1361);
R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-CH_2-C_6H_5$ (1350);
R^4 is-NH_2; R^5 is -CN; R^6 is -H; and R^7 is $-CH_2-CH=CH-CH_2-C_6H_5$ (1372); and
R^4 is $-NH_2$; R^5 is -CN; R^6 is $-NH_2$; and R^7 is $-CH_2-CH=CH-CH_2-C_6H_5$ (1329).

10. A pharmaceutical composition comprising a therapeutically effective amount of one or more compounds of claims 1, 2, 3, 4, or 5 and a pharmaceutically acceptable carrier.

11. A method for treating or preventing a viral infection comprising administering an effective amount of one or more compounds of any of claims 1 to 5 to a subject.

12. The method of claim 10, wherein the virus is a herpes virus, or hepatitis B virus or hepatitis C virus.

13. Use of least one of the compounds of any of claims 1 to 5, for the preparation of a medicament for the prevention or treatment of a viral infection.

14. A method for identifying a compound having anti-viral activity, comprising:
(a) contacting a cell infected with the virus with a candidate compound; and
(b) assaying the cell for inhibition of viral proliferation or infectivity by comparing the anti-viral activity against the anti-viral activity of a compound of claim 1, thereby identifying a compound having anti-viral activity.

15. A method for determining which compounds of claim 1 provided enhanced inhibition of viral replication or infectivity of a viral infection in a subject, the method comprising:

(a) contacting a sample isolated from the subject infected with the virus with one or more compounds of claim 1; and

(b) determining which compounds provide enhanced inhibition of viral replication or infectivity.

INTERNATIONAL SEARCH REPORT

Interr ...al Application No
PCT/US 00/00578

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/519 A61P31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 23151 A (THE REGENTS OF THE UNIVERSITY OF MICHIGAN) 31 August 1995 (1995-08-31) page 9, line 29 -page 12, line 24; examples 3D-I,4D-I,5D-I ---	1,10
A	US 4 892 865 A (LEROY B. TOWNSED ET AL.) 9 January 1990 (1990-01-09) cited in the application the whole document ---	1,10
A	US 4 968 686 A (LEROY B. TOWNSEND ET AL.) 6 November 1990 (1990-11-06) cited in the application the whole document ---	1,10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 June 2000	28/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kyriakakou, G

2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	THOMAS E. RENAU ET AL.: "Synthesis of Non-nucleoside Analogs of Toyocamycin, Sangivamycin, and Thiosangivamycin: Influence of Various 7-Substituents on Antiviral Activity" JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 4, 1996, pages 873-880, XP002139583 the whole document ---	1-15
A	THOMAS E. RENAU ET AL.: "Synthesis of Non-nucleoside Analogs of Toyocamycin, Sangivamycin, and Thiosangivamycin: The effect of Certain 4- and 4,6- Substituents on the Antiviral Activity of Pyrrolo‘2,3-d!pyrimidines" JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 18, 1996, pages 3470-3476, XP002139584 the whole document ---	1-15
A	PRANAB K. GUPTA ET AL.: "Synthesis, Cytotoxicity, and Antiviral Activity of some Acyclic analogues of the Pyrrolo‘2,3-d!pyrimidine Nucleoside Antibiotics Tubercidin, Toyocamycin, and Sangivamycin" JOURNAL OF MEDICINAL CHEMISTRY, vol. 32, no. 2, 1989, pages 402-408, XP000914555 cited in the application the whole document ---	1-15
A	PRANAB K. GUPTA ET AL.: "synthesis, Cytotoxicity, and Antiviral Activity of Certain 7-[2-Hydroxyethoxy)methyl!pyrrolo‘2,3-d!pyrimidine Nucleosides Related to Toyocamycin and Sangivamycin" JOURNAL OF MEDICINAL CHEMISTRY, vol. 32, no. 7, 1989, pages 1420-1425, XP000914556 cited in the application the whole document ---	1-15
A	SHARON M. BENNETT ET AL.: "Synthesis and Antiviral Activity of some Acyclic and C-acyclic Pyrrolo‘2,3-d!pyrimidine Nucleoside Analogues" JOURNAL OF MEDICINAL CHEMISTRY, vol. 33, no. 8, 1990, pages 2162-2173, XP000914557 cited in the application the whole document -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/00578

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 9523151	A	31-08-1995	AU	1882295	A	11-09-1995
			CA	2184199	A	31-08-1995
			EP	0746559	A	11-12-1996
			JP	10509132	T	08-09-1998
			US	5543413	A	06-08-1996
			ZA	9501509	A	08-12-1995
US 4892865	A	09-01-1990	NONE			
US 4968686	A	06-11-1990	US	4927830	A	22-05-1990
			US	RE36187	E	06-04-1999